Modern Methods for Total Synthesis of Important Oxindole Alkaloids

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ABSTRACT: This review describes the latest synthetic methods found in the literature for the construction of complex natural products containing the spiro[pyrrolidine-3,3′-oxindole] ring system and other oxindoles that are closely related. The spirooxindole system is the central structure of many different types of natural products and synthetic drugs, which are associated with various biological activities. The well-known interest that these compounds inspire in academia, as well as in industry together with our efforts toward the total synthesis of sarpagine-/macroline-related oxindoles inspired us to review this topic. Herein, the strategies used by other expert groups in the field of synthetic organic chemistry and their results are presented in a critical way. The examples were selected on the basis of the elegant way chemists resolved their synthetic challenges. Many other excellent syntheses of complex oxindoles can be found in the literature, but were not included due to the limit in the length of this manuscript.

KEYWORDS: spirocyclic oxindoles, oxindole alkaloids, alstonia oxindoles, cross coupling reactions, spirocyclic rearrangements, new synthetic methods

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1 Introduction

The spiro[pyrrolidine-3,3′-oxindole] ring system is the key structural fragment in a large group of bioactive natural products. These oxindole alkaloids are not only attractive for their biological activity but are also greatly appreciated targets for total synthesis due to their complex architecture. The amount of research effort applied to oxindoles from many groups around the world is represented by the ever-larger number of peer-reviewed articles found in the literature.[1a–d]

The purpose of this review was to collect the latest total syntheses of oxindole alkaloids that are believed to be more relevant to the advancement of the field and would best help to put in perspective the chemical research endeavor realized by our group. It is important to mention at this point that, to limit the length of this manuscript, many interesting oxindole syntheses were not included. The focus of this review was to describe the most important synthetic features of different approaches to complex oxindoles that really highlight how organic chemists, from several groups, resolved their problems, utilizing the latest chemistry. In this manner, the reader can have a much better understanding of which way the field is moving. The biological aspects of the target molecules were not mentioned, again to limit the length of this manuscript; however, the interested reader can easily find such information through the reference section.

2 Recent Total Synthesis of Alkaloids Containing the Spiro[pyrrolidine-3,3′-oxindole] Ring System

2.1 Hiemstra et al's total synthesis of corynoxine, corynoxine B, corynoxeine, and rhynchophylline. A racemic total synthesis of spirocyclic oxindole alkaloids corynoxine **13**, corynoxine B **18**, corynoxeine **17**, and rhynchophylline **19** was recently reported by Hiemstra et al.[1e] The Fukuyama procedure (Scheme 1)[2] was chosen for the selective synthesis of secondary amine **5**. In this way, tryptamine **1** was first converted to its *p*-nitrosulfonyl derivative, which was then alkylated with allylic bromide **2** to furnish sulfonamide **3**. Oxindole **4** was generated by treatment of **3** with *N*-chlorosuccinimide in aqueous THF under carefully controlled conditions in excellent yield. The sulfonyl group was removed from the nitrogen atom to give the secondary allylic amine **5** in four steps from tryptamine **1** in 73% overall yield.

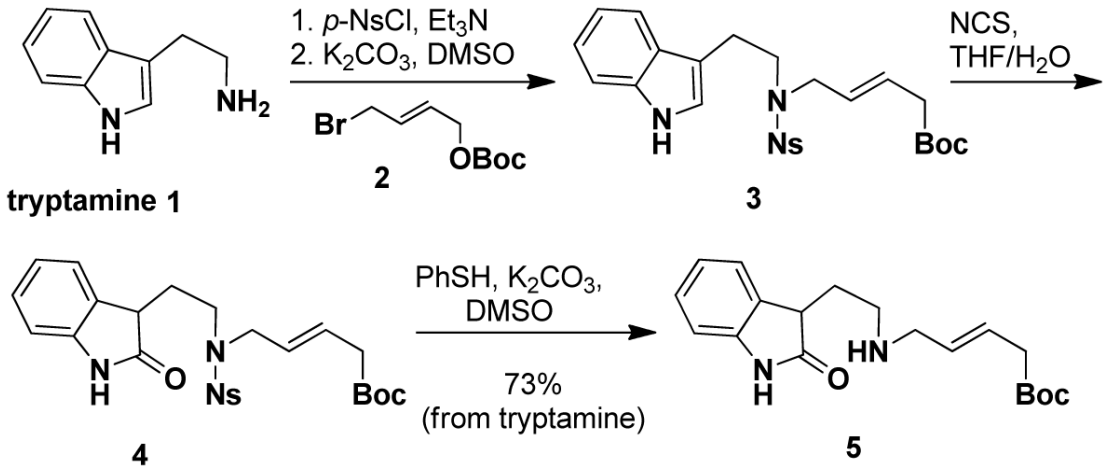
The key Mannich condensation reaction between equimolar amounts of amine **5** and aldehyde **6** proceeded in an anhydrous mixture of acetonitrile and triethylamine at room temperature to give a 1:2 mixture of spiro diastereomers **7** and **8**, respectively, in 75% yield (Scheme 2).

When minor diastereomer **7** was subjected to a reaction with 3 equivalents of a 1:1 molar mixture of cesium carbonate and diethylisopropylamine in the presence of 5 mol% of a palladium catalyst [allylpalladium chloride dimer as the Pd source with 1,2-bis(diphenylphosphanyl)ethane (dppe) as ligand], a Tsuji–Trost cyclization reaction occurred to give the *cis* product **9** in 63% yield (Scheme 3).[3]

The *trans* product could not be isolated in a detectable amount. The mixture of the two bases was important to achieve a good yield; the soluble amine base picked up the proton from the substrate, and it was then irreversibly trapped by the carbonate. Next, the *tert*-butyl ester moiety in **9** was transformed into its methyl ester **10**, principally because the *tert*-butyl ester was fully unreactive toward the Wittig reagent for the introduction of the methoxymethylene group. The transesterification reaction proceeded with only 57% yield because of some epimerization at C-15. The methyl ester **10** reacted to produce only the *Z* alkene **11**, which isomerized cleanly to give the more stable *E* isomer **12** under acidic, anhydrous conditions. Finally, hydrogenation gave racemic corynoxine **13**.[4]

The same series of reactions was applied to the major spirocyclization product **8**, as shown in Scheme 4. Palladium-catalyzed Tsuji–Trost allylic alkylation led to a 4:1 *cis/trans* mixture of cyclization products **14** and **15** in 56% and 14% isolated yields, respectively. In a similar way to that shown in Scheme 3, these tetracycles were converted to the target racemic natural products corynoxine B **18**,[4] corynoxeine **17**,[5] and rhynchophylline **19** (Scheme 4).[5]

2.2 Wang et al's enantioselective formal synthesis of rhynchophylline and isorhyncophylline. The protection of the primary alcohol moiety of aldehyde **22**, which was synthesized through the cross-metathesis of acrolein **21** and 3-butenol **20** with Grubbs' second-generation catalyst afforded the α,β-unsaturated aldehyde **23**, as illustrated in Scheme 5.[6] After an organocatalytic asymmetric Michael addition of methylmalonate to unsaturated aldehyde **23**, diester **26** was afforded as a crude product, which was used directly in the subsequent cascade reaction. Condensation of 2-chlorotryptamine **27** with **26** produced Schiff base **28**, which upon treatment with trifluoroacetic acid afforded the key spiral tetracyclic core (**29a**/**29b** = 3:1 dr) in 78% combined yield, with excellent enantioselectivity (**29**, 95% ee) from 2-chlorotryptamine **27**.



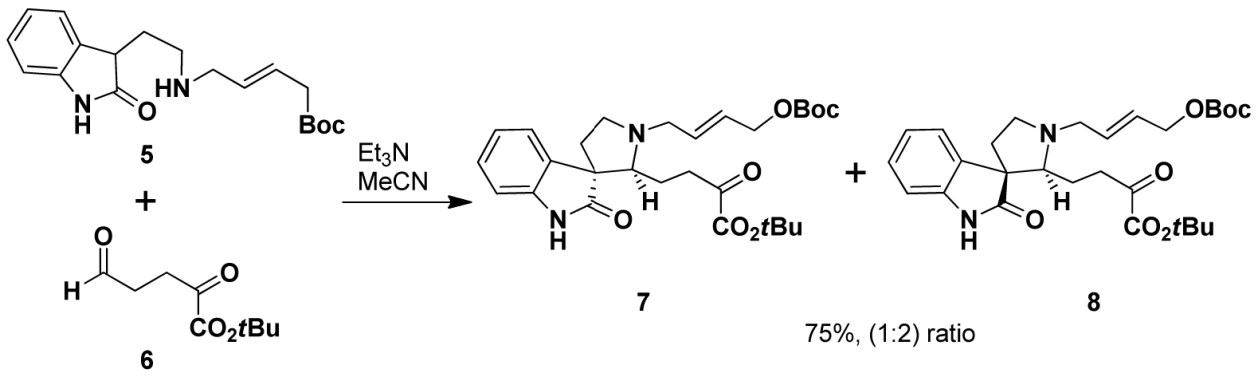
Scheme 1. Fukuyama procedure for the synthesis of N_b-allyl oxindole **5**.

It is important to note that **23** could be converted to the desired configuration through the subsequent steps, and no other stereoisomers were observed. In this regard, the observed stereochemistry during the formation of **29** could be rationalized through two chair-like transition states, as shown in Scheme 5. The destabilizing axial interactions would preclude the diastereomers epimeric at C-3, and the strong repulsion between the chlorine and hydrogen resulted in the exclusive formation of the C-7 epimer.

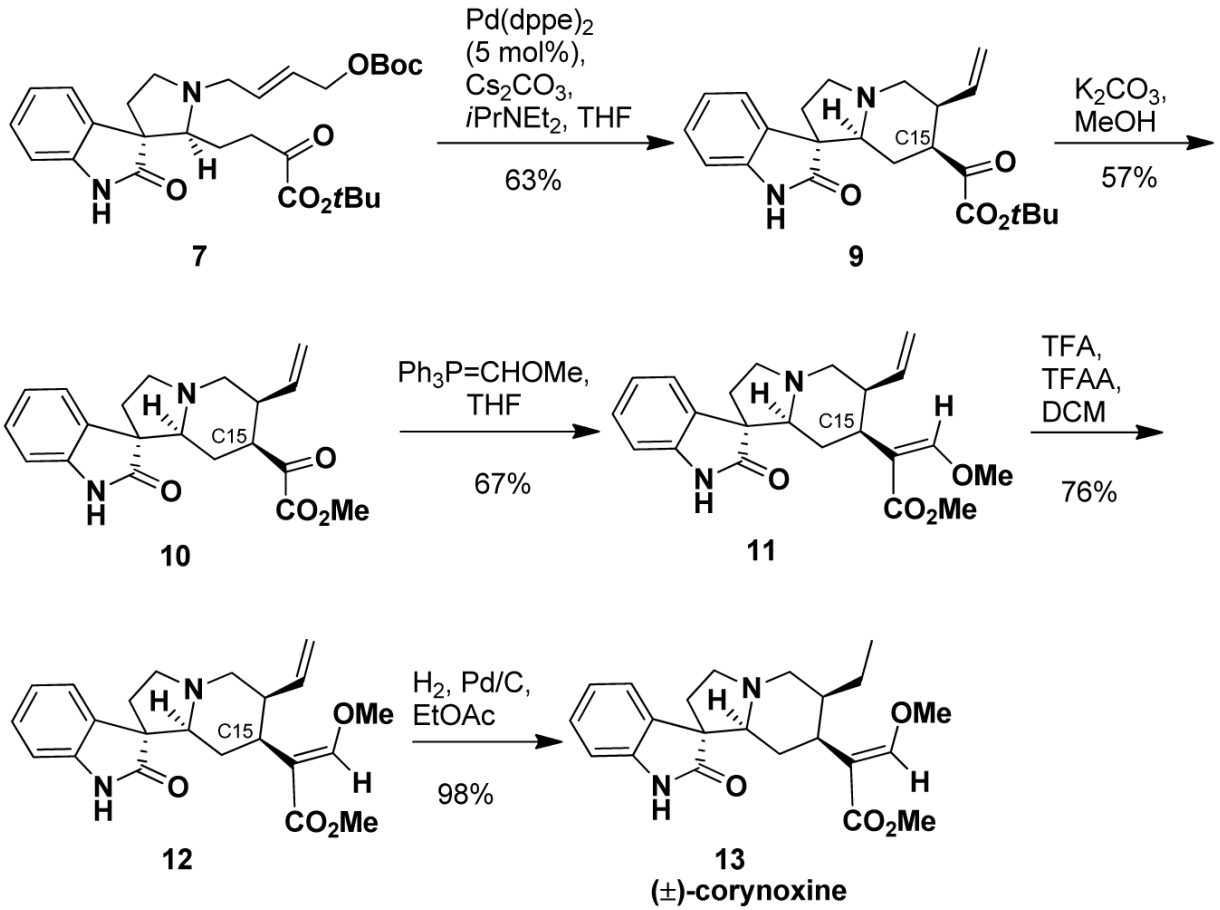
Next, the protection of diastereomeric mixture **29** with $(Boc)_2O$ and a subsequent conversion of the lactam ester to the thiolactam **30** with Lawesson's reagent proceeded in 74% yield over two steps (Scheme 6). Oxindole **30** was then treated with Raney nickel to furnish α,β-unsaturated ester **31** in 80% yield. The C-C double bond was reduced by means of cyanoborohydride in acetic acid to afford the stereoisomeric **32a** and **32b** (1:3.5 dr, respectively) in 79% combined yield. The Boc-protected oxindoles **32** were successfully deprotected with TFA in DCM, to give diastereomeric oxindoles **33a** and **33b** in 90% overall yield. The stereoisomer **33a** was epimerized to the desired configuration by treatment with potassium *tert*-butoxide in tetrahydrofuran (THF) in 70% yield (Scheme 6).

The chemoselective reduction of the ester **33b** with DIBAL-H, followed by an oxidation with IBX in DMSO and Wittig olefination, provided olefin **34** in 59% yield over three steps (Scheme 7). Desilylation with tetrabutylammonium fluoride (TBAF) in THF afforded the primary alcohol **35** in 96% yield. Accordingly, oxidation of the primary alcohol with IBX produced an aldehyde, which was subjected to Pinnick oxidation and esterification to afford ester **36** in 61% overall yield. Reduction of the double bond in oxindole **36** by Pd/C-catalyzed hydrogenation in methanol afforded tetracyclic oxindole **37** in 98% yield, which had been converted to both isorhynchophylline **38** and rhynchophylline **19** in two and three steps, respectively, according to the reported procedures (Scheme 7).[7]

2.3 Amat et al's enantioselective formal synthesis of *ent*-rhynchophylline and *ent*-isorhynchophylline. An enantioselective formal synthesis of *ent*-rhynchophylline and *ent*-isorhynchophylline was accomplished starting from (*S*)-tryptophanol **39** (Scheme 8).[8] (*S*)-Tryptophanol **39** had



Scheme 2. Mannich reaction for the synthesis of oxindole **8**.



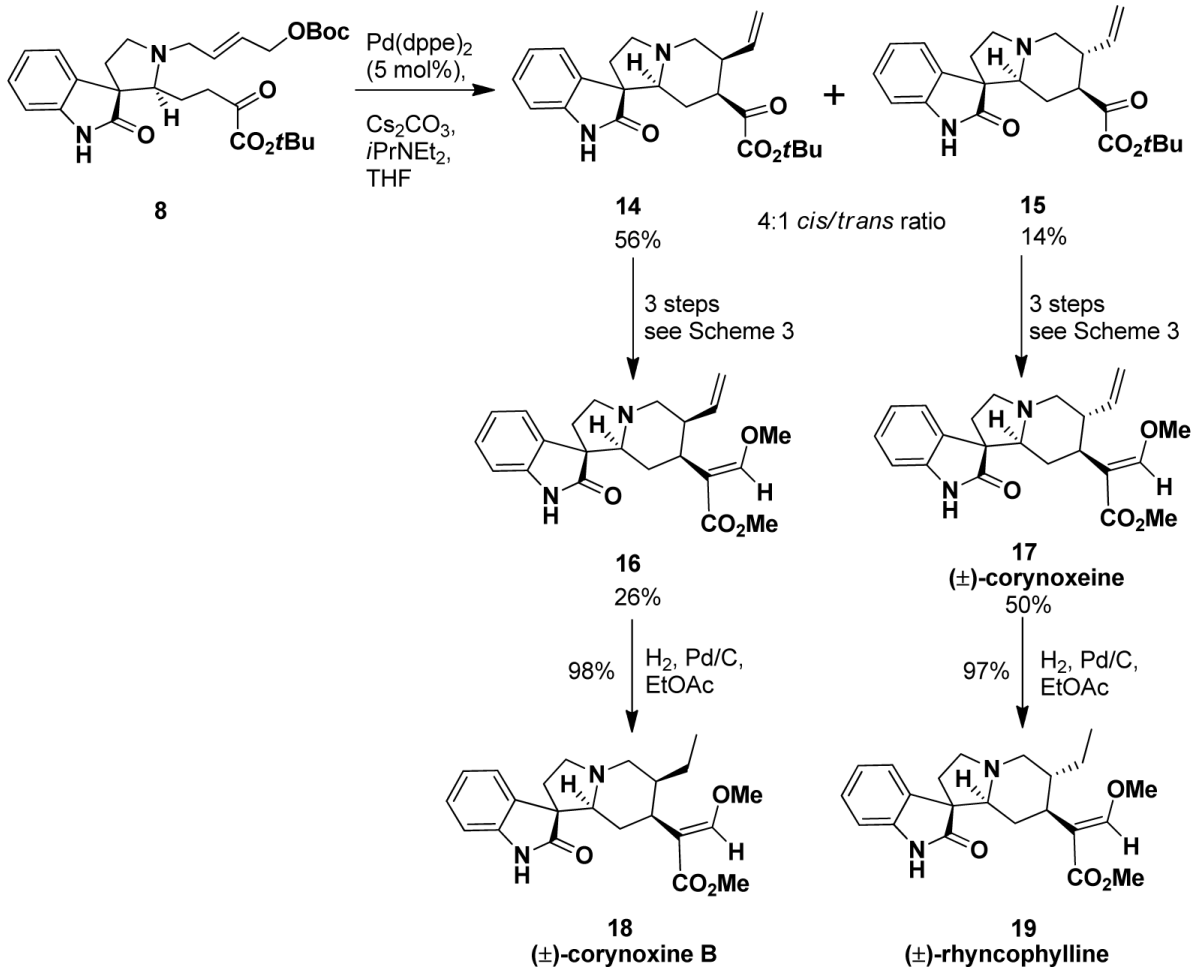
Scheme 3. Synthesis of corynoxine **13**.

the advantage that it not only acted as the source of chirality but also incorporated the tryptamine moiety present in several natural products. The synthesis that featured the stereoselective cyclocondensation and the spirocyclization of an *N*-benzenesulfonyl tryptophanol-derived oxazolopiperidone lactam **42** as the key steps is shown in Scheme 8. Cyclocondensation of (*S*)-tryptophanol **39** with the prochiral aldehyde-diester **40** led to the required bicyclic lactam **41**, in a process that involved the enantioselective desymmetrization of two enantiotopic chains. To direct the key cyclization at the indole 3-position, the *N*-indole was protected with the deactivating group benzenesulfonyl.

Treatment of lactam **42** with $TiCl_4$ in the presence of Et_3SiH resulted in a regio- and stereocontrolled cyclization, with concomitant reduction of the initially formed spiroindoleninium intermediate, leading to the tetracyclic spiroindoline **43** as a single stereoisomer in 93% yield (Scheme 8). For the enantioselective formal synthesis of *ent*-rhynchophylline and *ent*-isorhynchophylline (Scheme 9), it was necessary to (1) remove the hydroxymethyl group, (2) introduce stereoselectively the C-20 ethyl substituent, (3) oxidize the indoline moiety to the oxindole functionality, and (4) finally, reduce chemoselectively the lactam carbonyl.[7]

2.4 Fukuyama et al's stereoselective synthesis of spirotryprostatin A. Fukuyama et al reported the stereoselective synthesis of spirotryprostatin A **72** by employing an intramolecular Heck reaction to introduce the quaternary spirocenter.[9] The synthesis started from proline derivatives **51** and **52**, which reacted to form intermediate **55** via aldol condensation, followed by dehydration and then diastereoselective hydrogenation from the presumed convex face of the diketopiperazine. Treatment of ketone **55** with TBSOTf and Et_3N furnished silyl enol ether **56** in 99% yield (Scheme 10).

The alkyl group at C-18 was introduced by Mukaiyama aldol reaction (Scheme 11) with silyloxy acetaldehyde **57**. The resulting mixture of aldols was dehydrated by treatment with Tf_2O and pyridine, which led to the unsaturated ketone **58** in 87% yield as a 6.6:1 mixture of the *E/Z* isomers. Diketopiperazine **59**, with the desired C-18 (*S*) stereochemistry, was obtained after hydrogenation of the double bond. Then, the TIPS-protected alcohol **60** was obtained after a three-step sequence that involved the addition of vinylmagnesium bromide to **59**, treatment with thionyl bromide, and reduction of the rearranged allyl bromide with $LiEt_3BH$. It was known that a tethering unit containing an arylketone moiety



Scheme 4. Synthesis of corynoxeine **17**, corynoxine B **18** and rhyncophylline **19**.

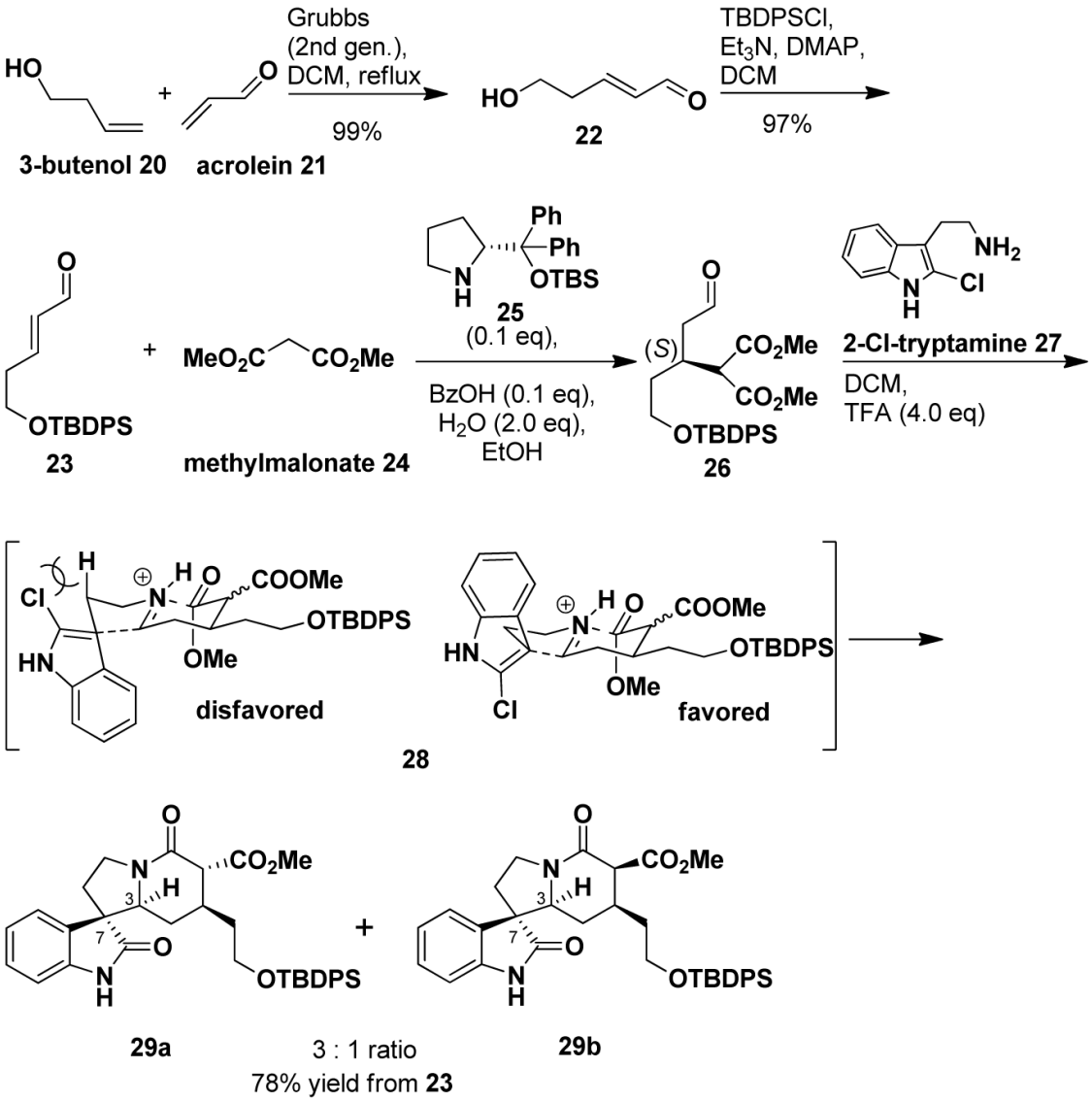
has proven to work well for the Heck reaction. Thus, removal of the TIPS group, followed by oxidation of the primary alcohol, gave the aldehyde **62**, to which was added the aryl Grignard reagent. The desired tethered ketone **64**, required for the intramolecular Heck reaction, was obtained after Dess–Martin oxidation. As a consequence of this tether, the aryl moiety approaches selectively from the desired face, leading to the ketone **65** in 96% yield.

For the construction of the spiroindolinone moiety (Scheme 12), ketone **65** was converted to oxime mesylate **67**. Treatment of pentacyclic oxime mesylate **67** with $TiCl_4$ triggered a Beckmann rearrangement to afford lactam **69**, after introduction of a Boc group. Addition of MeLi led to opening of the lactam to afford the tertiary alcohol **70**. Ozonolysis of the vinyl group, followed by reaction with aniline, gave a five-membered hemiaminal, which after oxidation gave spiroindolinone **71**. Spirotryprostatin A (**72**) was obtained in 91% yield after dehydration of the tertiary hydroxyl group and removal of the Boc group under acidic conditions (Scheme 12).

2.5 Zhao et al's synthesis of racemic corynoxine and corynoxine B. Zhao et al developed a straightforward method for the construction of the fused tetracyclic 3-spirooxindole skeleton, which exists widely in natural products.[10] To highlight the utility of the direct cross-dehydrogenative coupling, two natural products, namely, (±)-corynoxine **13** and (±)-corynoxine B **18**, were synthesized from the coupling product **76**, as shown in Schemes 13 and 14. The pyridinium salt **75** was obtained by the treatment of 3-(2-bromoethyl)indolin-2-one **73** with 1-(pyridin-3-yl) ethanone **74**. Subsequently, the transition-metal-free cross-dehydrogenative coupling was performed using optimized conditions: Na_2CO_3 as the base, acetonitrile (polar solvents worked best), molecular oxygen as oxidant, and the temperature was set at 50°C (otherwise the reaction would proceed slowly, see Scheme 13).

Next, the coupling product, oxindole **76**, was treated with $NaBH_4$ in a mixture of dioxane and water (20:1); subsequently, the pyridinium and the ketone groups were reduced to afford the oxindole alcohol **77**, as illustrated in Scheme 14.

Although no selectivity was observed at the newly formed hydroxyl group, it did not affect the efficiency of the total synthesis because both of the isomers afforded the same final product. The alcohol **77** was then subjected to Johnson–Claisen



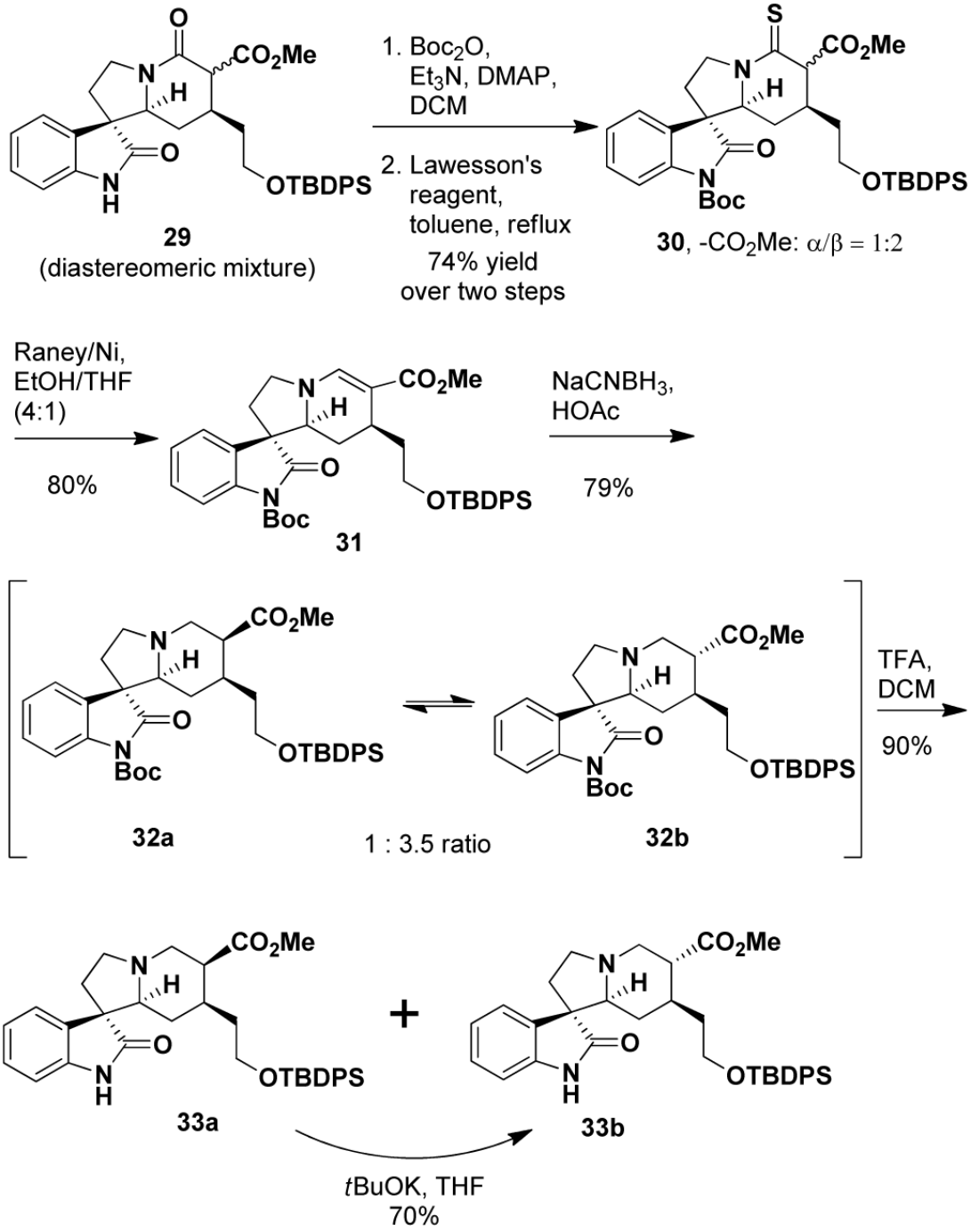
Scheme 5. Synthesis of oxindole intermediate **29**.

rearrangement by heating with trimethyl orthoacetate in the presence of a catalytic amount of propanoic acid to afford the ester **78**.

Treatment of the ester with lithium diisopropylamide (LDA), followed by the addition of excess methyl formate, resulted in the desired enol ester intermediate in 36% yield (82% based on recovered starting material [brsm]). The crude enol ester was later methylated with trimethylsilyl diazomethane to give **79** in 62% yield. Finally, the catalytic hydrogenation of **79** utilizing PtO_2 under a hydrogen atmosphere afforded the target compound, namely, (±)-corynoxine **13**, in 86% yield. Dissolution of (±)-corynoxine **13** in 2,2,2-trifluoroethanol led to the formation of epimeric (±)-corynoxine B **18** in six hours. Chromatographic separation of the mixture afforded a 90% yield of (±)-corynoxine B **18** along with recovered (±)-corynoxine **13** (31%). Clear evidence for this equilibrium ratio was found, when (±)-corynoxine B **18** was subject to the identical conditions and the same ratio was reached between (±)-corynoxine **13** and (±)-corynoxine B **18** within six hours.

2.6 Hayashi et al's synthesis of (–)-horsfiline and (–)-coerulescine by asymmetric organocatalyzed Michael addition of nitromethane to a 2-oxoindoline-3-ylidene acetaldehyde. Hayashi et al recently reported the three one-pot sequential syntheses of both (–)-horsfiline **93** and (–)-coerulescine **94** by employing two key reactions, namely, (1) the synthesis of a 2-oxoindoline-3-ylidene acetaldehyde from acetaldehyde **81** and an isatin derivative **80** and (2) the organocatalyzed Michael addition of nitromethane to the 2-oxo-indoline-3-ylidene acetaldehyde **83** to construct the all-carbon quaternary stereogenic centers with excellent enantioselectivity (Scheme 15).[11]

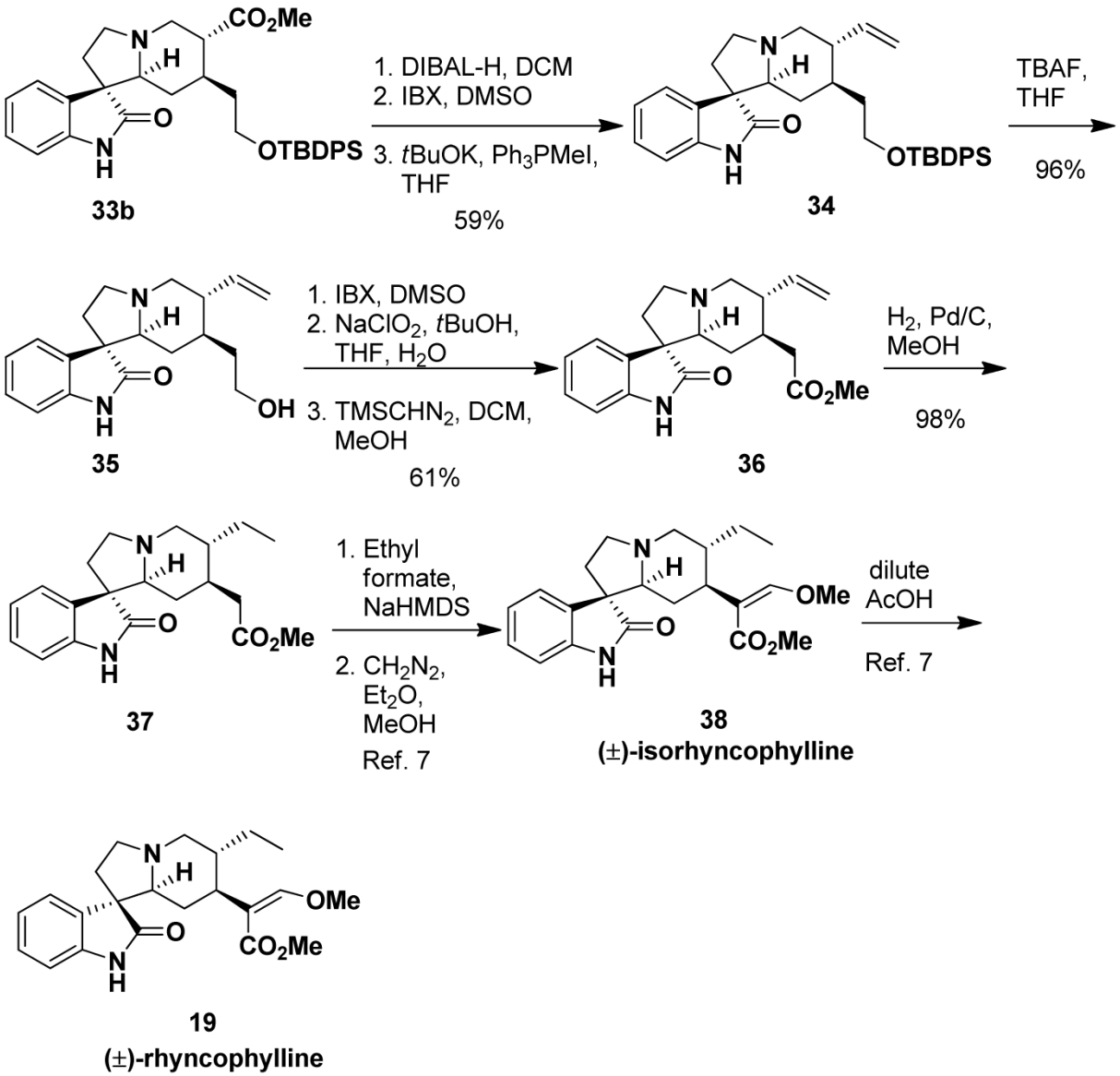
The synthesis started with the aldol addition of isatin derivative **85** with acetaldehyde **81**, which generated the



Scheme 6. Synthesis of oxindole intermediate **33b**.

β-hydroxyaldehyde **86** and subsequent dehydration under acidic conditions, provided the 2-oxoindoline-3-ylidene acetaldehyde **87** (or **88**) directly as a mixture of *E/Z* isomers (Scheme 16). The enals were both obtained in a one-pot operation from the corresponding isatins in excellent yield. This method was found to be higher yielding and more convenient than the reported methods.[11]

The enantioselective conjugate addition of nitromethane to **87** (or **88**) generated aldehydes **90** with excellent enantioselectivity in the construction of the all-carbon quaternary stereogenic centers (Scheme 17). Zn, AcOH, and water were then added to the same reaction vessel to reduce the nitro group into an amine. At the same time, an intramolecular reductive amination proceeded to form the pyrrolidino spirocycle **91**. Formaldehyde was then added to the reaction mixture sequentially to install the *N*-methyl group by an intermolecular reductive amination. This afforded **92a** and **92b** in 46% and 69% yield, respectively, in four steps from their corresponding aldehydes. The four reactions from aldehydes **87** (or **88**) were performed in the same reaction



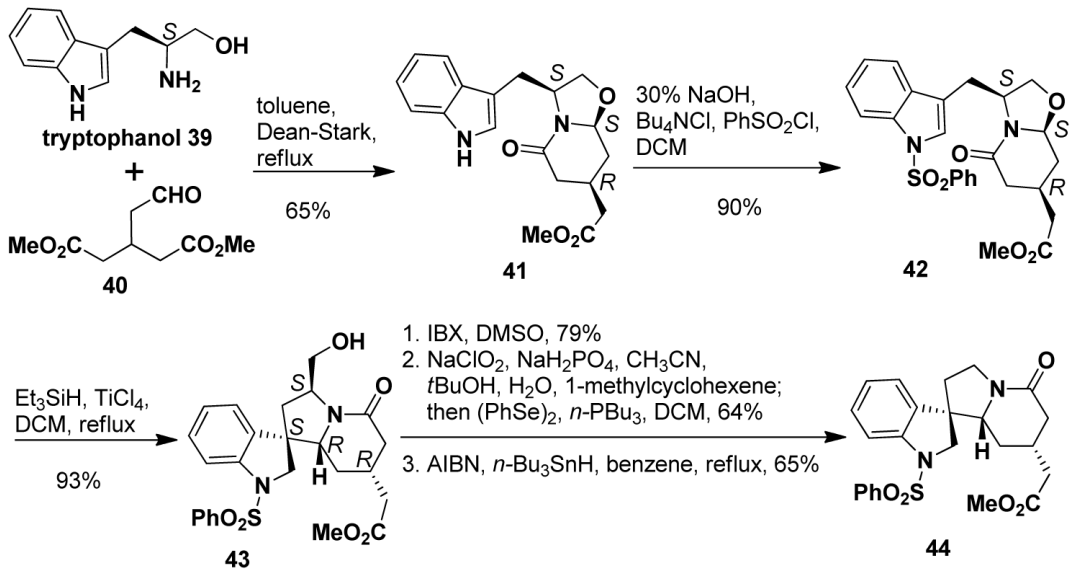
Scheme 7. Synthesis of isorhyncophylline **38** and rhyncophylline **19**.

vessel. The removal of the benzyl group under Birch conditions furnished (*R*)-horsfiline **93** and (*R*)-coerulescine **94** in good yields. The spirooxindole group tends to racemize under acidic conditions; therefore, the optical purity was checked by HPLC analysis over a chiral phase. This showed that the ee values of **93** and **94** were 95% and 94%, respectively, which indicated that racemization did not occur during the synthesis (Scheme 17).

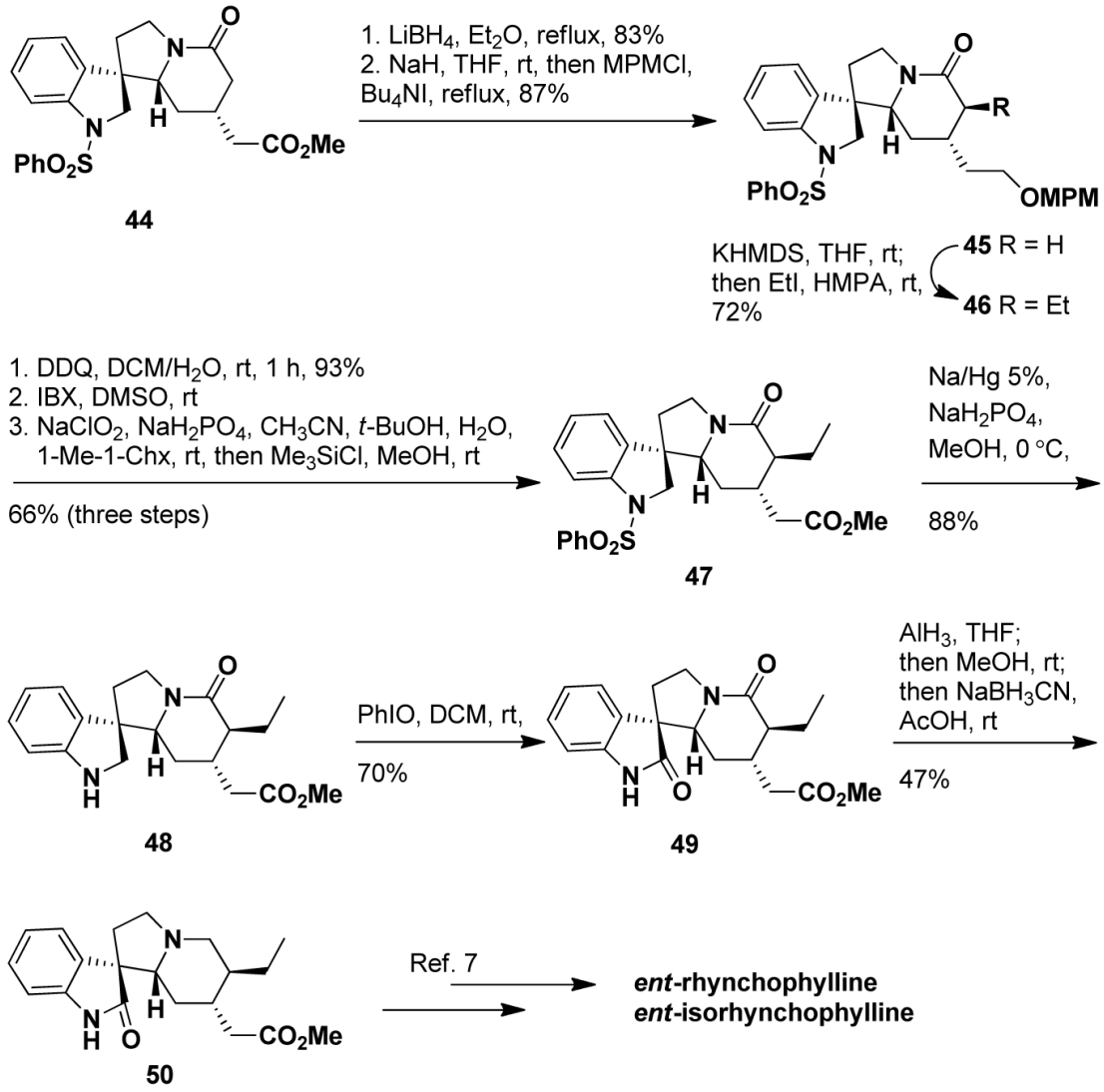
It should be noted that excellent enantioselectivity was observed even though a mixture of *E*/*Z* isomers of ylidene aldehydes **87** (or **88**) was used. It is assumed that isomerization between the *E* and *Z* isomers would occur through the addition and elimination of a hydroxy ion, as illustrated in Scheme 18.

The proposed transition state models for Michael addition of a nitronate anion into the iminium salts are shown in Figure 1. The nitronate ion approaches the iminium salts via the acyclic synclinal transition state proposed by Seebach and Golinski, which maximizes the electrostatic interaction between the nitro group and iminium ion. The *Z* isomer reacts to provide the major enantiomer in **TS-1**. On the other hand, there is a steric repulsion between the phenyl group and the nitro group at the synclinal position in **TS-2**. As a result, it is believed that the addition of nitromethane proceeds preferentially via **TS-1** to form the major enantiomer.

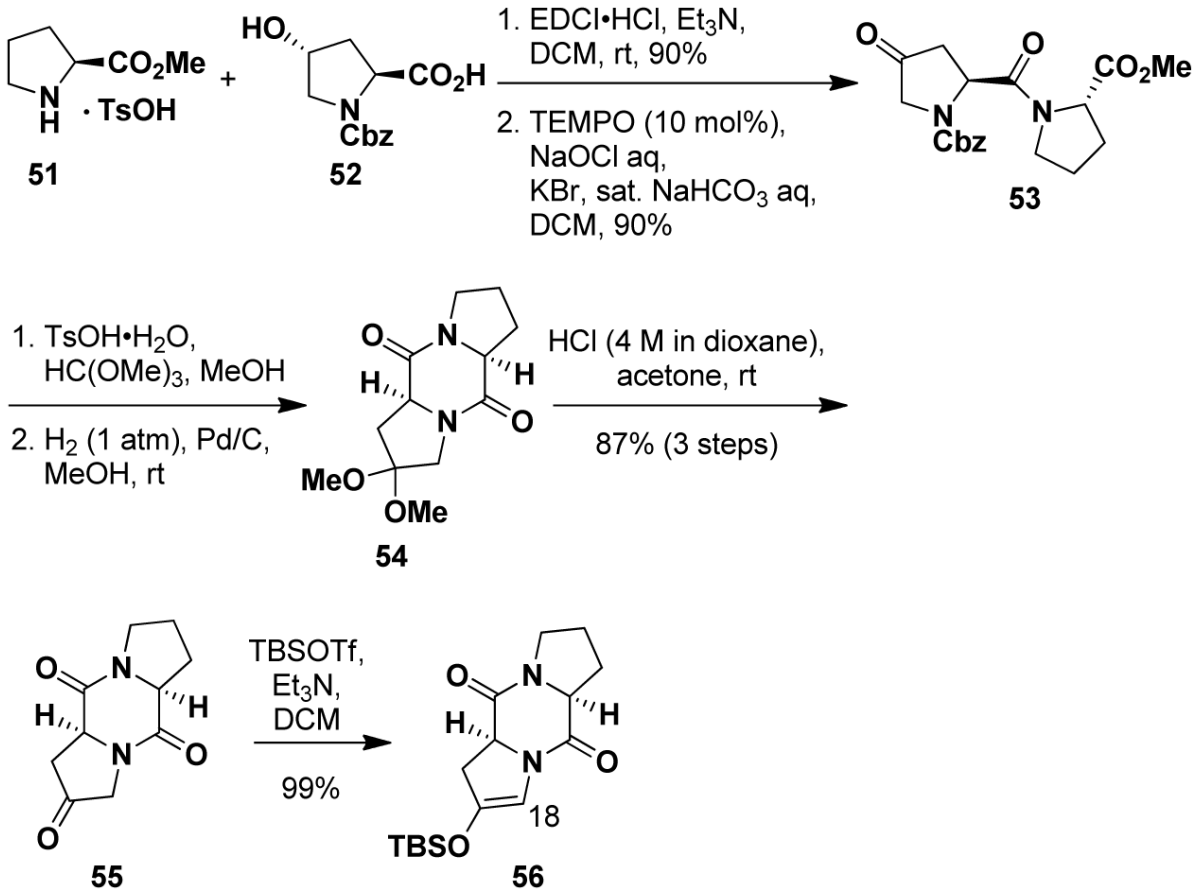
2.7 Park et al's enantioselective phase-transfer catalytic total synthesis of (–)-horsfiline. Park et al reported an efficient synthetic method for the preparation of (–)-horsfiline **93** through the enantioselective phase-transfer catalytic (PTC) α-allylation of malonate.[12] First, substrate **100** for the enantioselective PTC α-allylation was prepared from



Scheme 8. Synthesis of intermediate **44**.



Scheme 9. Synthesis of oxindole **50** and final products.



Scheme 10. Synthesis of diketopiperazine intermediate **56**.

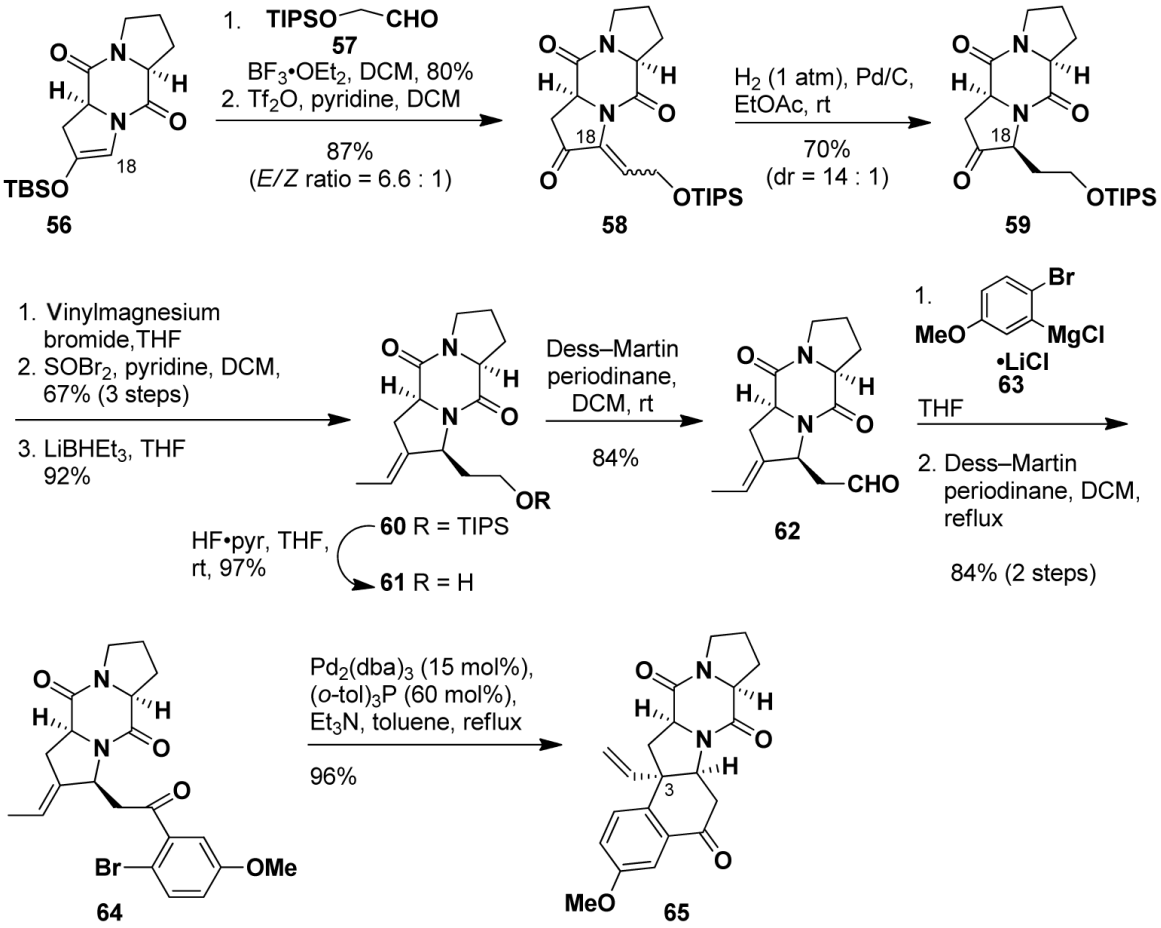
diphenylmethyl *tert*-butyl malonate (Scheme 19). Nucleophilic aromatic substitution with 2-fluoro-4-methoxy-1-nitrobenzene, under basic conditions (*tert*-BuOK) in dimethylformamide (DMF) at room temperature, afforded α-arylmalonate **100** (65% yield). Next, the PTC-mediated allylation of malonate **100** in the presence of (*S,S*)-3,4,5-trifluorophenyl-NAS bromide **101**, along with allyl bromide (5 equivalents) and 50% KOH (aq, 5 equivalents) at −40°C in toluene (Scheme 19), gave the allylated compound (*R*)-**102** with excellent yield and enantiomeric excess (99%, 91% ee).

Ozonolysis of **102**, followed by reductive workup in the presence of triphenyl-phosphine, afforded the corresponding aldehyde **103** (99%, Scheme 20). Aldehyde **103** was reduced by sodium borohydride in ethanol to provide lactone **104**.

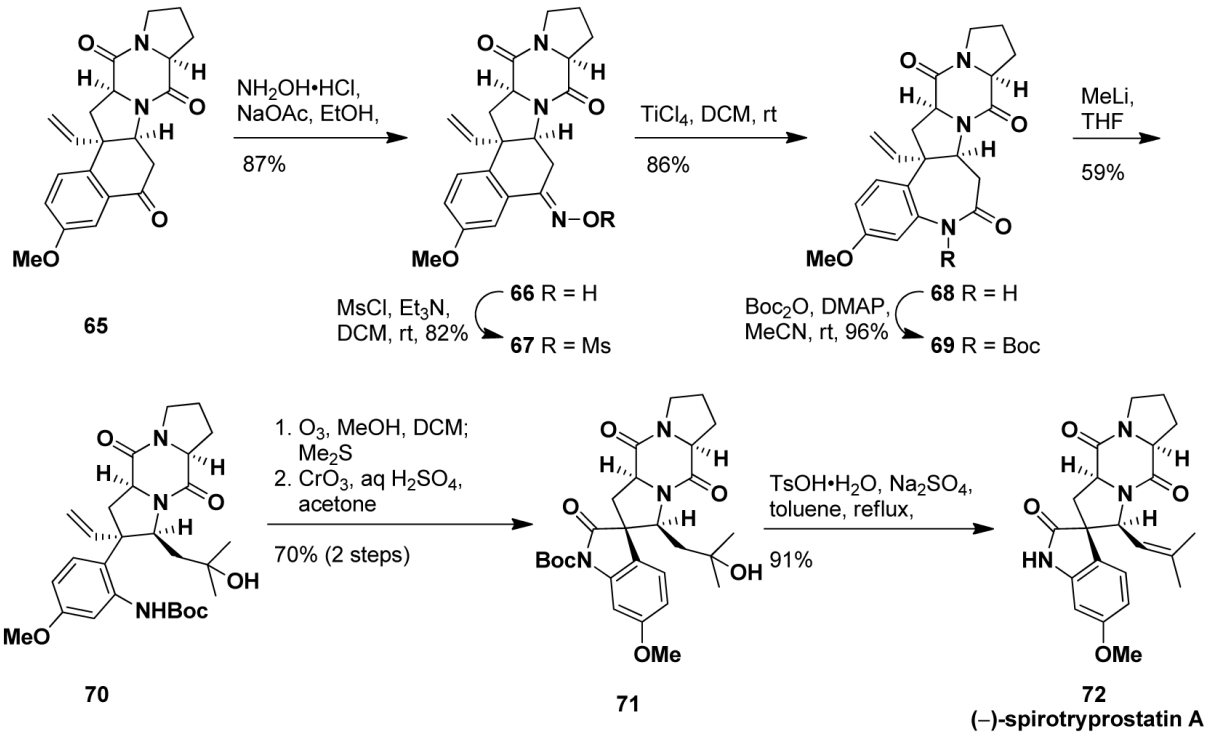
Without purification, the lactone moiety of **104** could be selectively reduced again to the corresponding diol **105** in situ by additional treatment of sodium borohydride with cerium(III) trichloride and THF as a cosolvent (61% from **103**). As a side reaction, removal of the α-hydroxymethyl group was partially observed by deformylation via a retro aldol reaction, caused by the α-nitrophenyl group. The major enantiomer of diol **105** could be easily purified as a single stereoisomer (>99% ee) in 85% yield by recrystallization using hexane and ethyl acetate (5:1). Dimesylation of diol **106** (99% yield), followed by double N-alkylation using excess methylamine, successfully afforded *N*-methylpyrrolidine **108** in 98% yield. The nitro group was easily reduced with H_2/Pd(C) in one hour to afford aniline **109**. Finally, (–)-horsfiline **93** was successfully obtained by stirring methylpyrrolidine **109** with silica gel (SiO_2) in CH_2Cl_2, without racemization (98%, >99% ee).[12]

2.8 Wearing et al's enantiospecific synthesis of (+)-alstonisine via a stereospecific osmylation process and proof of the absolute configuration of this natural product. Wearing et al reported an enantiospecific, stereospecific total synthesis of (+)-alstonisine **144**.[13a,b] The work established the correct absolute configuration of this natural oxindole alkaloid. It also confirmed its correct structure in agreement with that proposed by Le Quesne based on biogenetic grounds.[13c–15] This corrected the structure reported in a *J. Am. Chem. Soc.* communication, incorrectly drawn from an X-ray crystal structure by Nordman et al. A method that provided entry into a spirocyclic oxindole, diastereomeric at C-7, was developed in the course of this work as well.

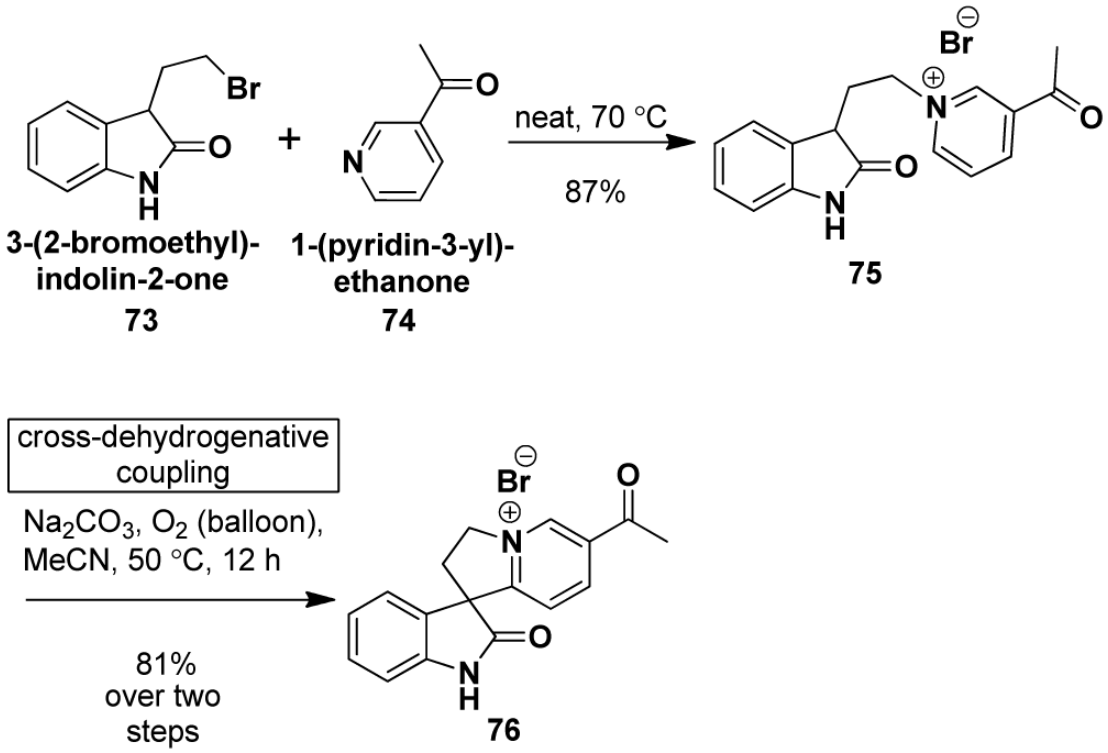
The synthesis of alstonisine **144** began with the preparation of the (–)-N_a-H, N_b-benzyl tetracyclic ketone **113** as the key building block on large scale (Scheme 21). The starting material D-(+)-tryptophan methyl ester **110** was diastereospecifically



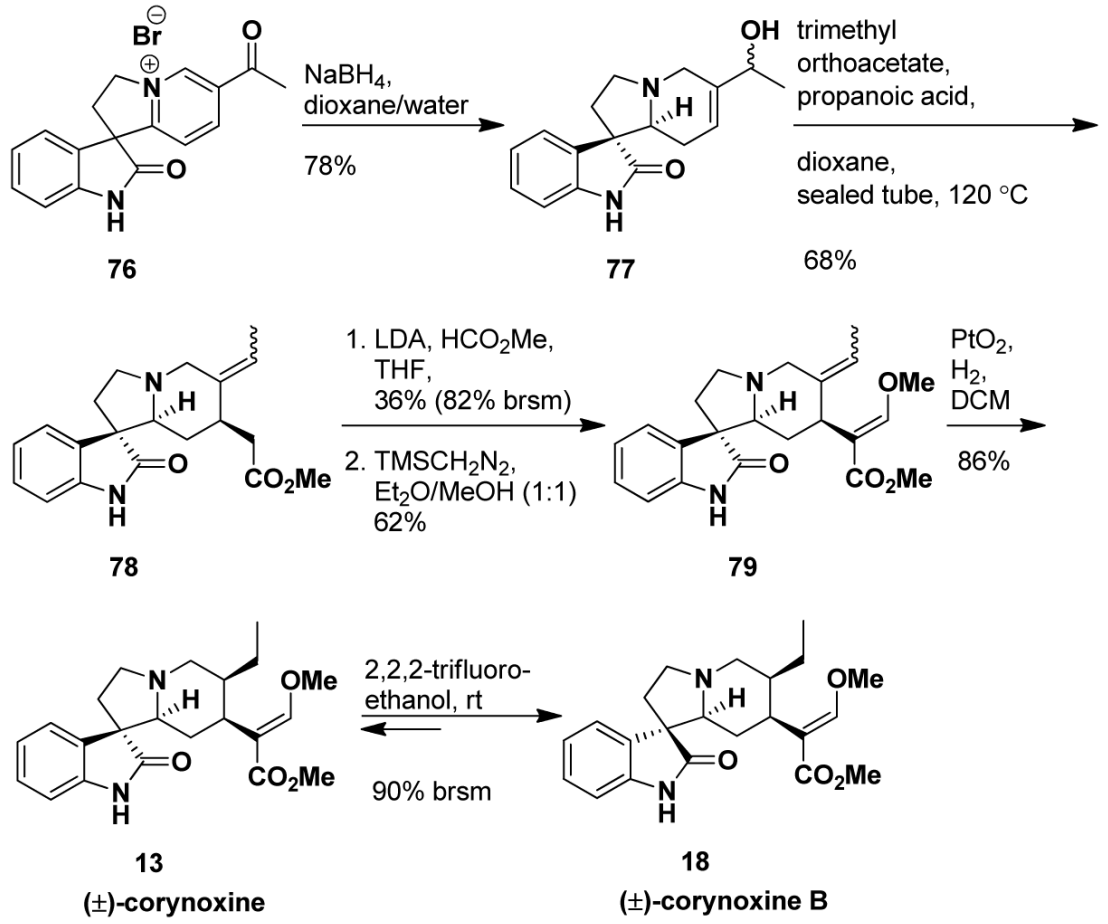
Scheme 11. Synthesis of ketone intermediate **65**.



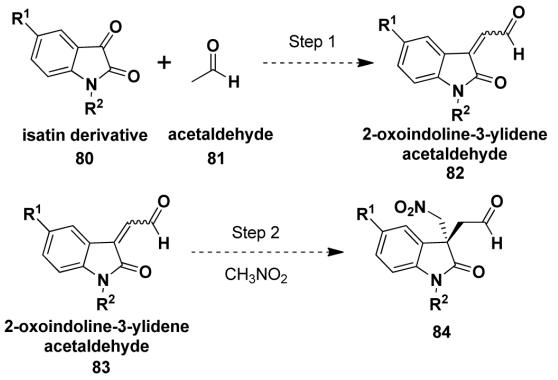
Scheme 12. Synthesis of (–)-spirotryprostatin A **72**.



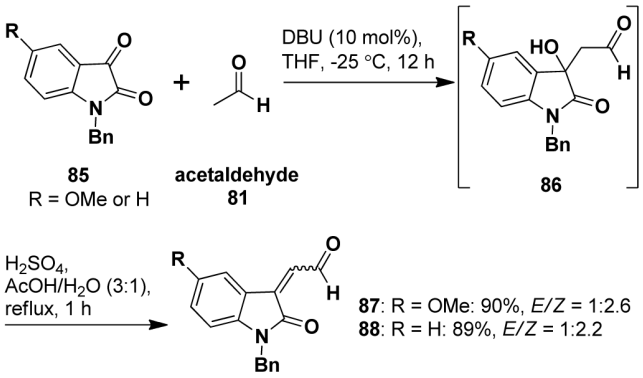
Scheme 13. Synthesis of oxindole **76**.



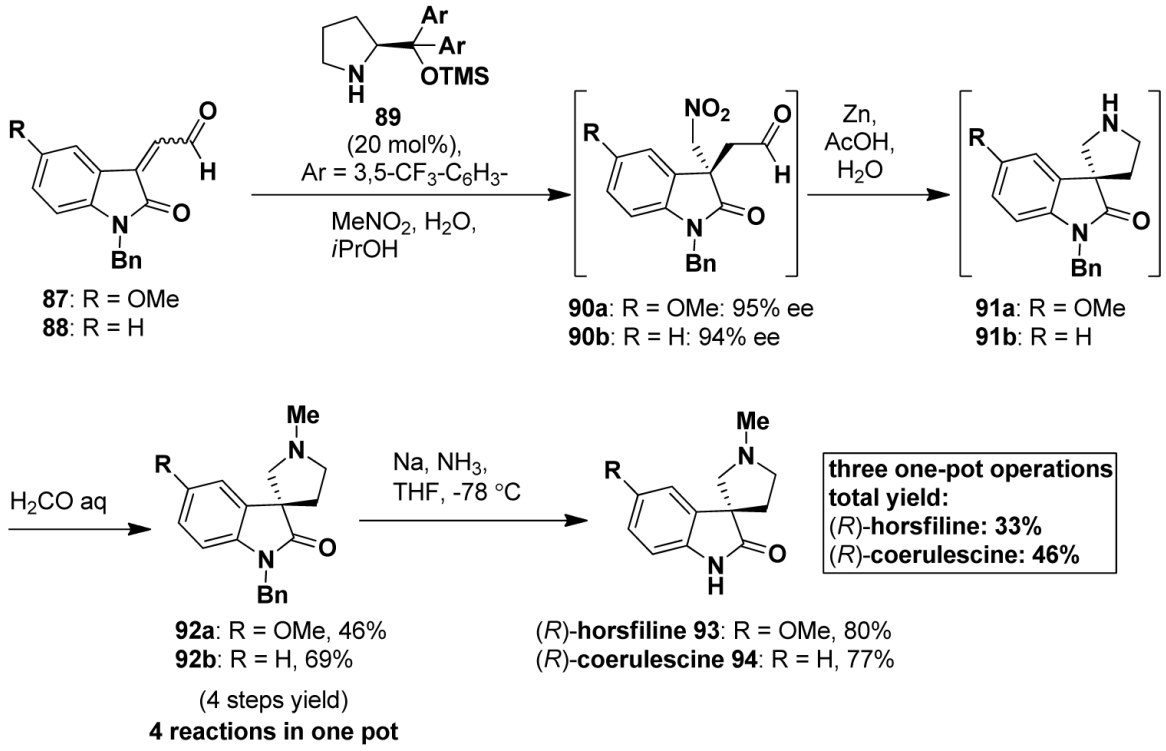
Scheme 14. Synthesis of corynoxine **13** and corynoxine B **18**.



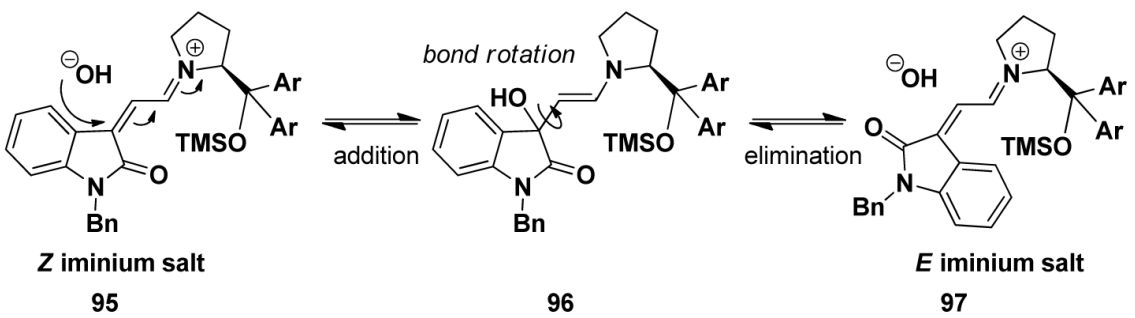
Scheme 15. Feature reactions in the synthetic route.



Scheme 16. Synthesis of acetaldehyde derivatives **87** and **88**.



Scheme 17. Synthesis of (*R*)-horsfiline **93** and (*R*)-coerulescine **94**.



Scheme 18. Proposed mechanism of isomerization between the *E* and *Z* isomers.

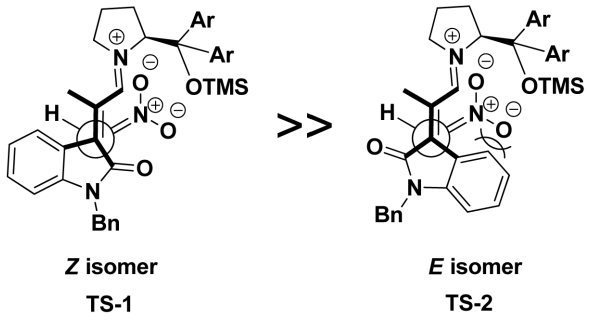


Figure 1. Michael addition of a nitronate anion into the iminium salts.

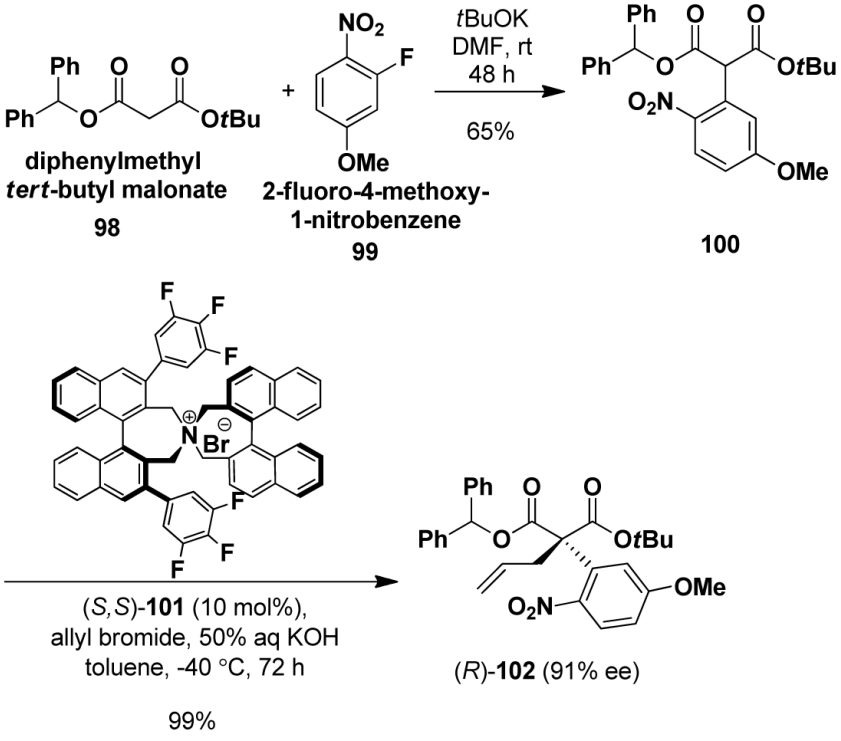
converted to azabicyclononone **113** in greater than 98% ee in a two-pot process on multihundred gram scale via tetrahydro-β-carboline **112**. After N_b-benzylation of the tryptophan methyl ester **110** with benzaldehyde and sodium borohydride in methanol was completed, at 0°C, trifluoroacetic acid was added to the reaction vessel at 0°C to neutralize the alkaline mixture. Removal of the solvent under reduced pressure was followed by the addition of CH_2Cl_2, TFA, and methyl 4,4-dimethoxybutanoate **111** to the vessel at 0°C, and the modified Pictet–Spengler reaction (600 g scale) was carried out to provide the *trans* diester **112** in 83% overall yield. In the second sequence of reactions (150 g scale), the Dieckmann cyclization was completed, and the reaction solution was then cooled to 0°C after which it was carefully quenched with glacial acetic acid. Concentrated glacial AcOH, aqueous HCl, and H_2O were added to the residue, after removal of the solvent under reduced pressure, in the same vessel at 0°C. The acidic hydrolysis and decarboxylation were then executed at reflux to provide (–)-**113** in 80% yield in greater than 98% ee.

After tetracyclic ketone **113** was constructed enantiospecifically, the α,β-unsaturated aldehyde (**117**, Scheme 22) was prepared. The conversion was achieved in good yield via the spirooxirane phenylsulfoxide **115** by the published methods of Satoh et al.[16a–c] The N_a-H tetracyclic ketone **113** was treated with the anion of α-chloro-methylphenyl sulfoxide generated in situ to furnish a chlorohydrin intermediate **114**. Treatment of **114** with aq 10 N KOH/THF (3:7) converted the crude chlorohydrin to spirooxirane phenylsulfoxide **115**. The spirooxirane phenylsulfoxides were then dissolved in a solution of dry dioxane, which contained lithium perchlorate.

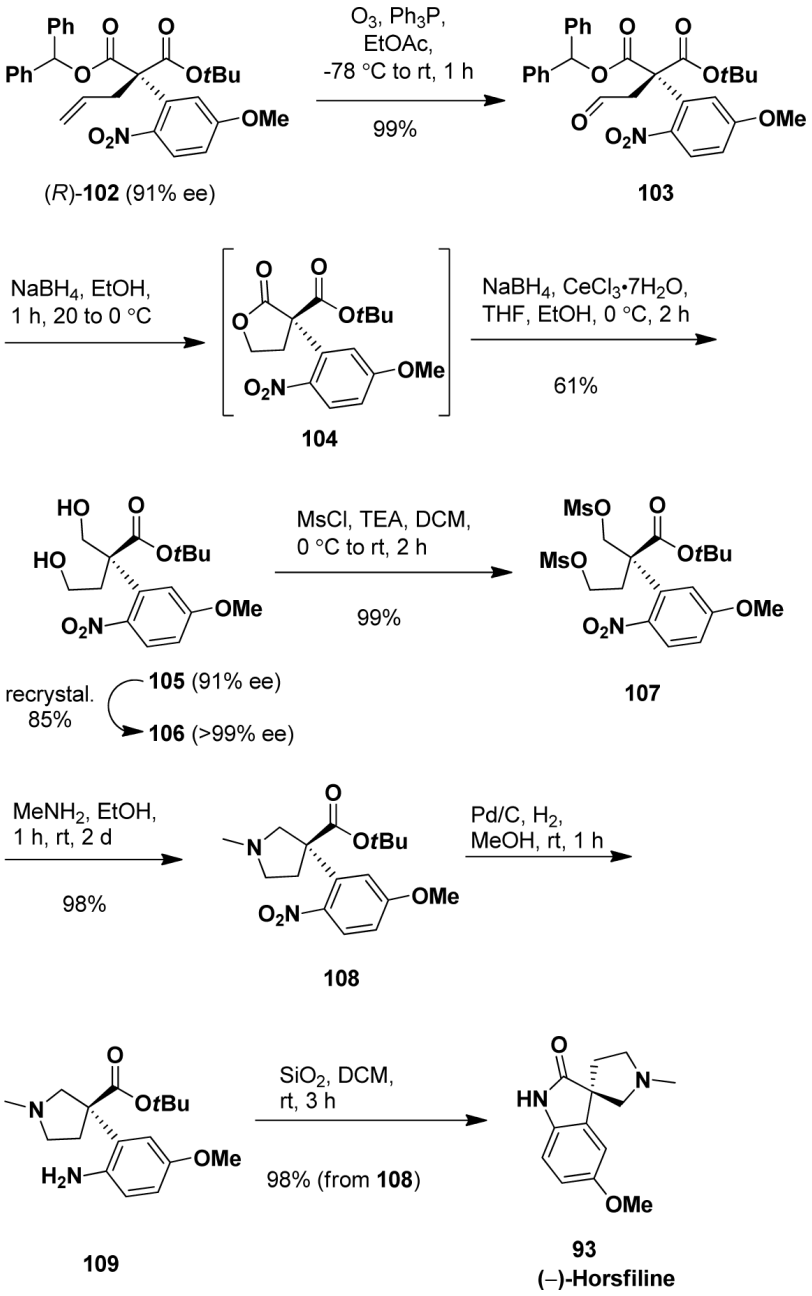
The slurry that resulted was heated under nitrogen to provide the desired α,β-unsaturated aldehyde (**117**, 87% overall yield, >98% ee). Dioxane was employed to dissolve the catalytic amount of lithium perchlorate, which permitted replacement of the original procedure (toluene) to avoid the use of tri-*n*-butylphosphine oxide. The phosphine oxide was difficult to remove after the reaction was complete; consequently, the use of dioxane/$LiClO_4$ was an important improvement in a practical sense.

In the mechanism for the formation of the α,β-unsaturated aldehyde (Scheme 22), the Lewis acid-catalyzed oxirane rearrangement was followed by a sulfoxide-mediated *syn* elimination to generate **117**.[13a–c]

In order to functionalize the C-15 position of the α,β-unsaturated aldehyde **117** and avoid allylic rearrangement of the allyl Grignard reagent, which was prepared from



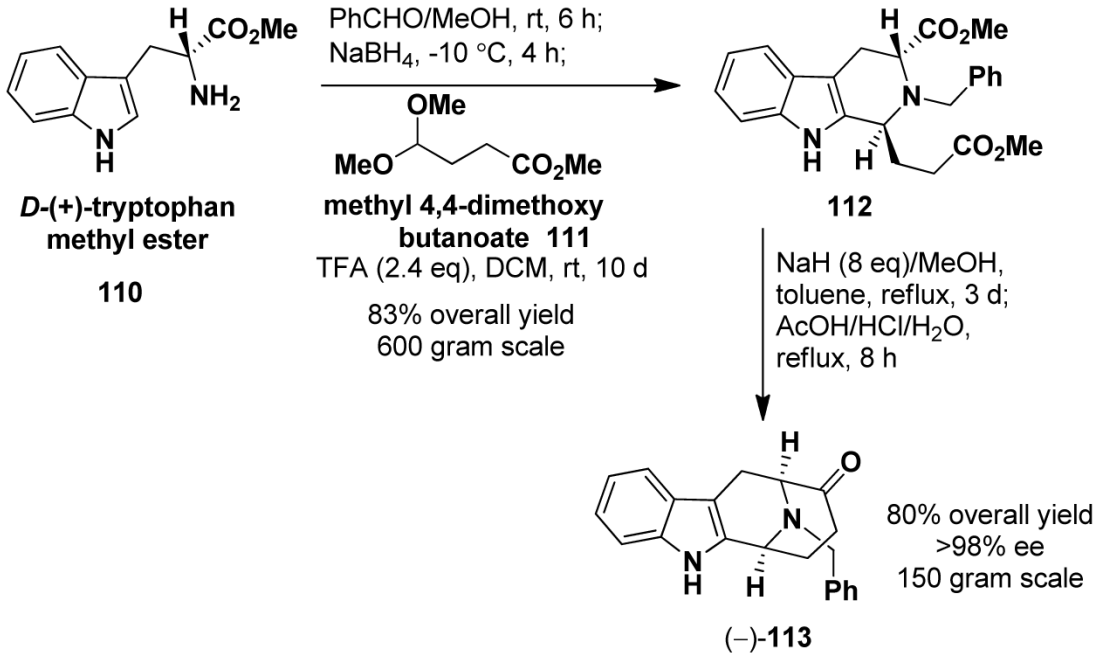
Scheme 19. Preparation of intermediate **102**.



Scheme 20. Synthesis of (–)-horsfiline **93**.

1-bromo-2-pentene, a barium-mediated 1,2-addition protocol was chosen (Scheme 23). Similar to the Barbier–Grignard process,[17,18a–c] with 1-bromo-2-pentene and Rieke barium, the modified Yamamoto procedure provided the desired allylic alcohol **119** in high yield. The reason for the high regioselectivity of the addition of the barium reagent through the α-carbon atom in this Barbier–Grignard process was believed to be due to the unusually long barium-carbon bond.[19a,b] The anionic oxy-Cope rearrangement took place in the N_a-H azabicyclononene system **119** almost exclusively from the desired bottom face of the C-15/C-16 olefinic bond, as expected, to afford olefin **120** in 88% overall yield. The diastereoselectivity at C-15 was greater than 30:1 in this system to provide the correct chirality at C-15. The purpose of adding methanol to the reaction mixture was to epimerize the newly formed aldehydic function at C-16 of the minor isomer into the more stable (desired) configuration. Then, when the olefinic aldehyde **120** was treated with sodium hydride and methyl iodide, an almost quantitative yield of the N_a-methyl olefinic aldehyde **121** was obtained, which was reduced with sodium borohydride in 95% yield to furnish monol **122** (Scheme 23).

Olefin **122** was next stirred with a premixed solution of OsO_4-pyridine in THF, oxidative cleavage of the olefinic unit occurred to give hemiacetal **124** in 78% yield. The intermediate aldehyde **123** that formed underwent cyclization simultaneously to form the desired E-ring, without affecting the

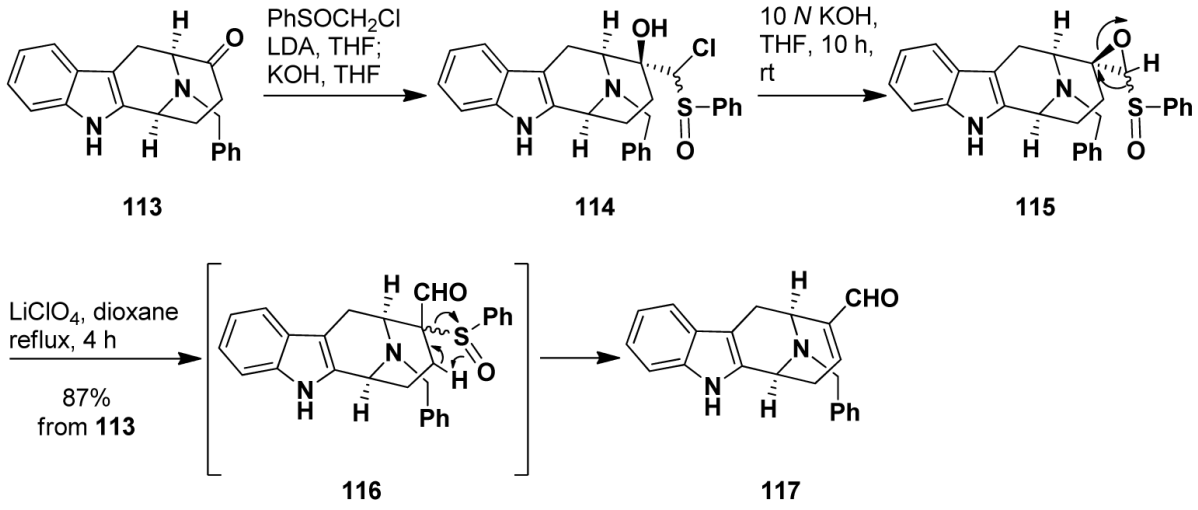


Scheme 21. Synthesis of tetracyclic ketone **113**.

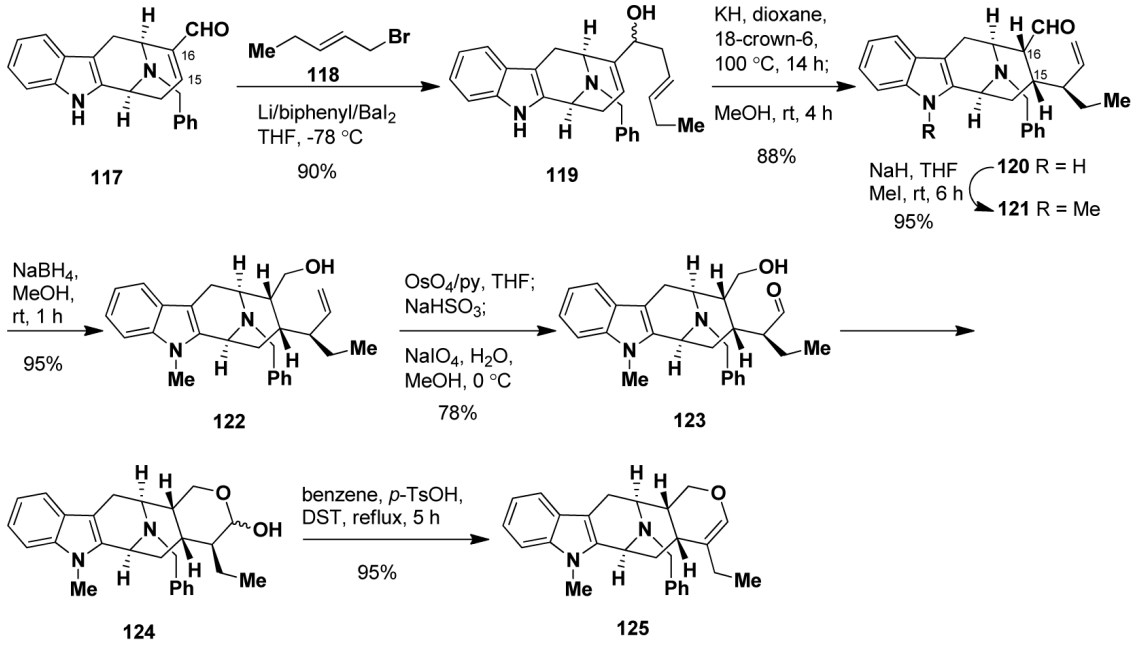
chirality at C-15 and C-16. The hemiacetal **124** was converted into a single pure enol ether **125** on dehydration with *p*-TSA in refluxing benzene (95% yield).

This macroline-related enol ether **125** was also obtained from the degradation of ajmaline **126** by a much improved modification of the procedures of Takayama et al[20] and Gan and Cook.[21] As illustrated in Scheme 24, the hydroxyl group at C-21 in ajmaline **126** was selectively protected in 85% yield with acetic anhydride to form the acetyl ester **127**. Oxidation of the indoline moiety with lead(IV) acetate generated the aldehyde **128** in 85% yield. Epimerization of the stereogenic center at C-16 with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dry THF provided the thermodynamically more stable aldehyde **129** in almost quantitative yield. Reduction of the aldehyde function in **129** with sodium borohydride afforded the primary alcohol **130** in high yield. Next, the macroline-related hemiacetal **131** was formed in 91% yield by treatment of the aminoacetate **130** with benzyl bromide in the presence of K_2CO_3.

Finally, dehydration of hemiacetal **131** in dry benzene at reflux in the presence of 1.1 equivalents of dry *p*-toluenesulfonic acid gave the N_b-benzyl enol ether **125** in very high yield (Scheme 24). The enol ether **125** that was obtained from the transformation of ajmaline **126** was



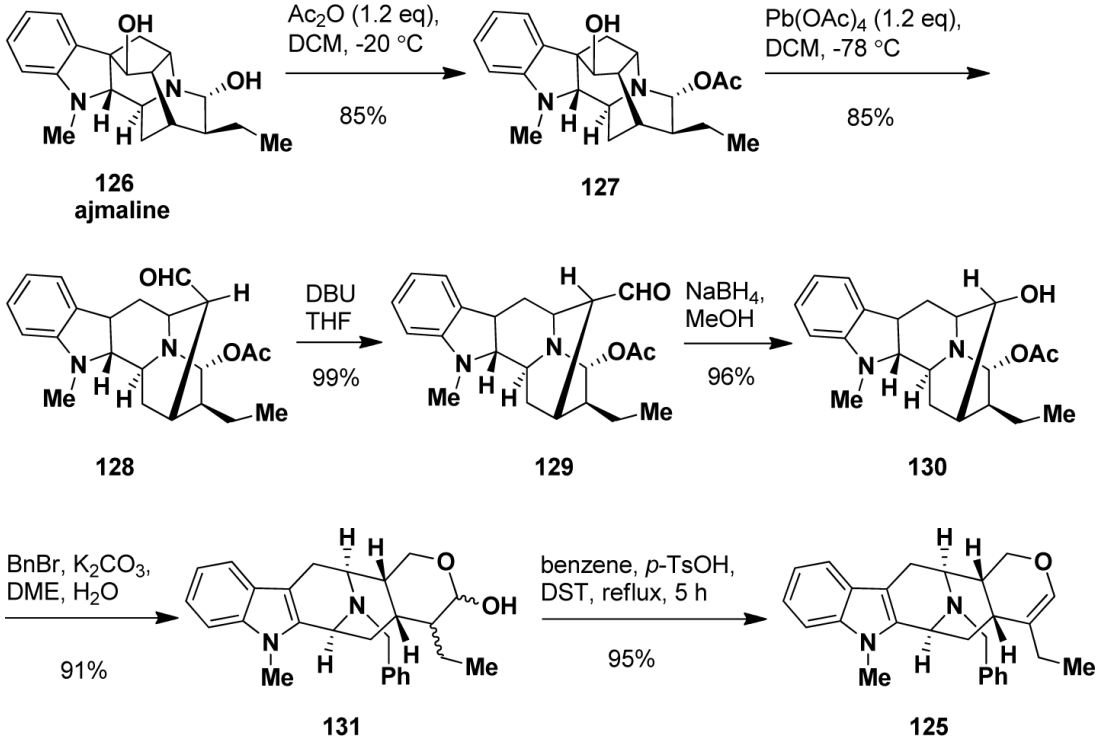
Scheme 22. Synthesis of tetracyclic enal **117**.



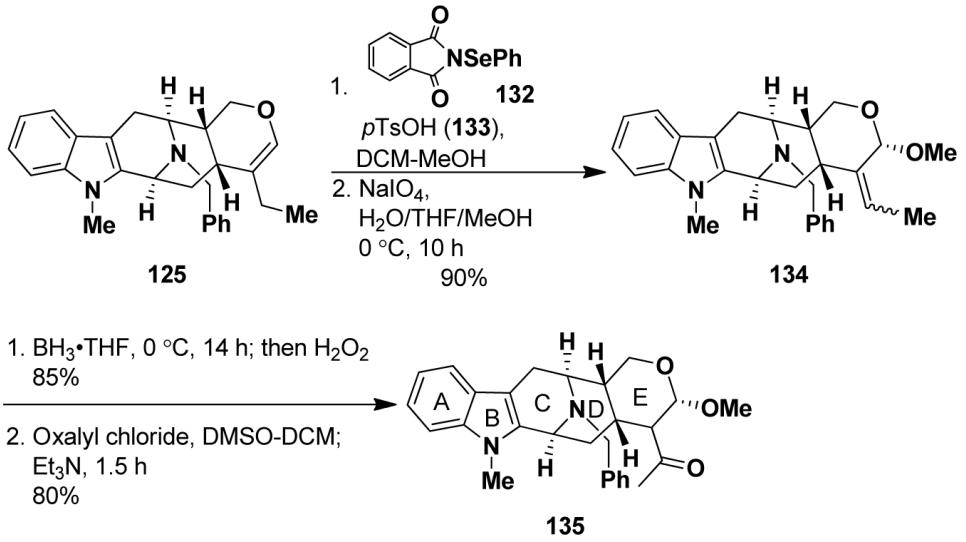
Scheme 23. Synthesis of pentacyclic enol ether **125**.

identical to the material prepared from olefinic aldehyde (**117**, Scheme 23).

The regiospecific oxyselenation of the olefin **125** was carried out with *N*-phenylseleno phthalimide **132** in CH_2Cl_2–MeOH in the presence of *p*-TSA **133** to provide a mixture of selenoacetals in high yield (Scheme 25). This mixture was directly treated with $NaIO_4$ in THF–MeOH–H_2O solution (without separation) to afford olefins **134** in 90% yield as a 4:1 mixture of *Z/E* isomers. Treatment of the mixture of olefins **134** with the BH_3·THF complex and H_2O_2 oxidation, followed by the modified Swern oxidation conditions, gave the ketoacetal **135** in 80% yield.



Scheme 24. Synthesis of pentacyclic enol ether **125** from ajmaline **126**.



Scheme 25. Synthesis of pentacyclic ketone **135**.

With the availability of intermediate **135**, Wearing et al decided to approach the synthesis of alstonisine **144**, in a stereocontrolled manner, to establish the correct chirality at C-7. Initially, the conversion of tetracyclic ketone **136** into either diastereomeric N_b-benzyltetracyclic oxindole (**139**, proposed alstonisine stereochemistry) or (**138**, Scheme 26) with stoichiometric amounts of osmium tetroxide in the presence or absence of Sharpless' ligands was executed by Peterson and Cook.[22] Excellent diastereoselectivity was obtained in this process. In the presence of OsO_4, **139** was the major diastereomer (91:9), but in the presence of OsO_4 with a Sharpless' ligand, the opposite diastereomer **138** was obtained (97:3). In the case of ketal **140**, only one diastereomer was formed in 80% yield (Scheme 26).

With this information in hand, a solution of ketoacetal **135** in THF–pyridine (5:1) was stirred with a premixed solution of osmium tetroxide (1 equivalent) in THF–pyridine (5:1) at room temperature (Scheme 27). This was followed by reductive workup with aqueous $NaHSO_3$. From this process, the ketoacetal oxindole **143** was obtained as the sole diastereomer in 81% yield. It was believed that the osmium tetroxide coordinated to the piperidine nitrogen atom, delivering the reagent from the convex face of the substrate intramolecularly (as shown in the model reactions in Scheme 26). This complexation was presumably favored because of the axial preference (with respect to the D-ring) of the benzyl group (as seen in **141**, Scheme 26). The concomitant complexation of osmium at the equatorial position (with respect to the D-ring) facilitated intramolecular attack of the osmium reagent to furnish osmate ester. The osmate ester was then reduced by sodium bisulfite, and the *cis*-diol that resulted underwent a pinacol rearrangement to furnish the desired oxindole (**143**, Scheme 27) diastereospecifically.

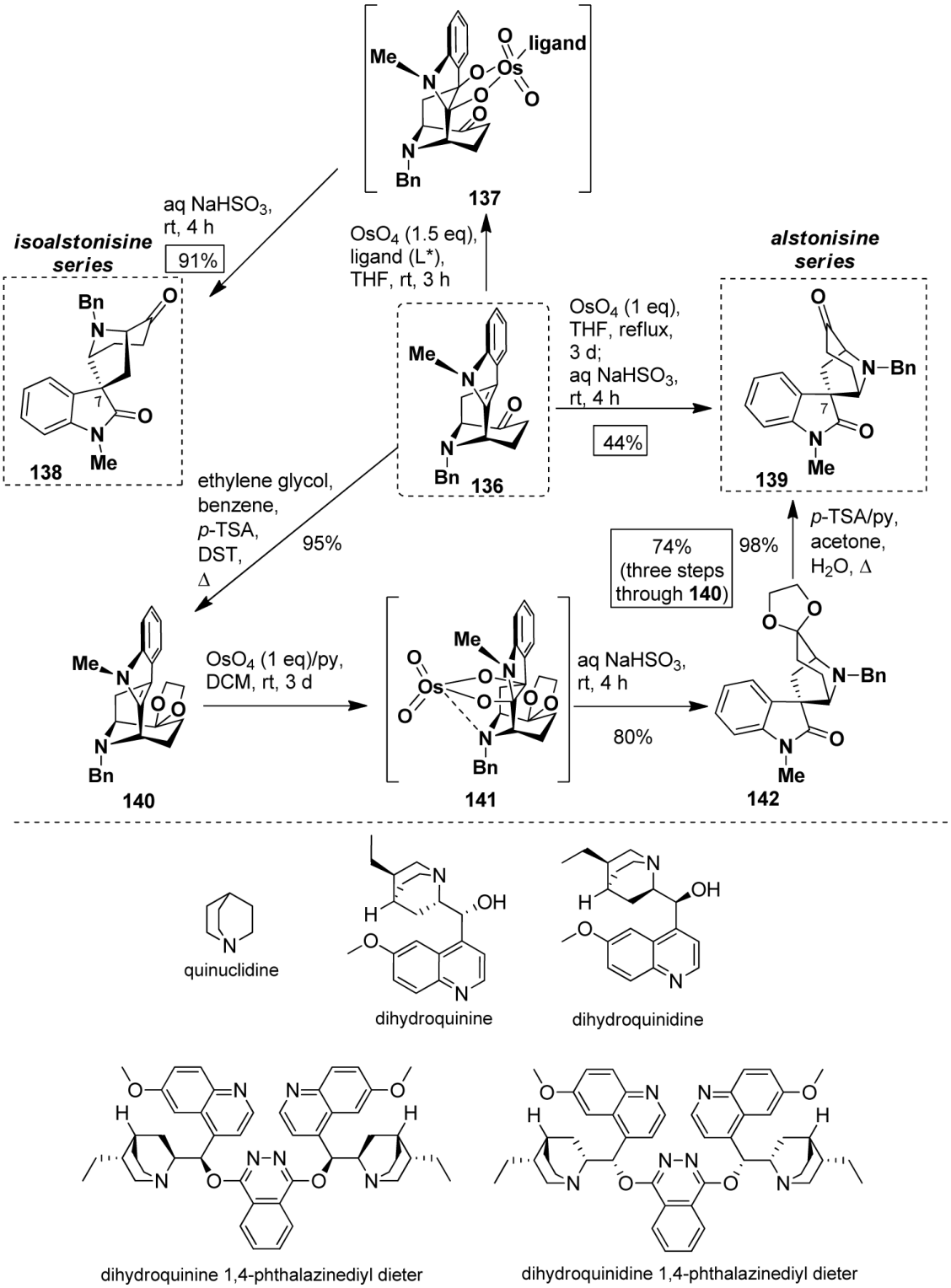
In the final stage of the synthesis, the benzyl group was successfully removed by hydrogenolysis when two equivalents of Pearlman's catalyst $[Pd(OH)_2/C]/H_2$ were used (Scheme 27). Base-mediated elimination of the elements of methanol was then carried out to furnish (+)-alstonisine **144** in 86% yield (two steps).

The first total synthesis of alstonisine was accomplished, by Wearing et al, in an enantiospecific fashion in an overall yield of 12% (from tryptophan methyl ester **110**) and in 17 reaction vessels. The structure and absolute configuration of (+)-alstonisine **144** at C-7 were determined by NOE-NMR spectroscopic experiments and were further confirmed by single-crystal X-ray analysis and comparison of the properties to natural alstonisine, kindly provided by Professor Le Quesne. This corrected the structure earlier reported by Nordman, which had been incorrectly drawn because the absolute configuration had been incorrectly correlated with that of ajmalacine.

3 Recent Advances in the Total Synthesis of Related Natural Oxindole Alkaloids

3.1 Carreira et al's total synthesis of (±)-gelsemoxonine. Carreira et al's reported a racemic total synthesis of gelsemoxonine **167** that utilized the ring contraction of a spirocyclopropane isoxazolidine as the key step to provide access to the azetidine moiety. An additional salient feature of the synthesis was the introduction of the congested quaternary oxindole stereocenter at C-7 by a diastereoselective reductive Heck cyclization. The route began with the construction of the pyran precursor **151** for the key ring contraction, as depicted in Scheme 28.[23]

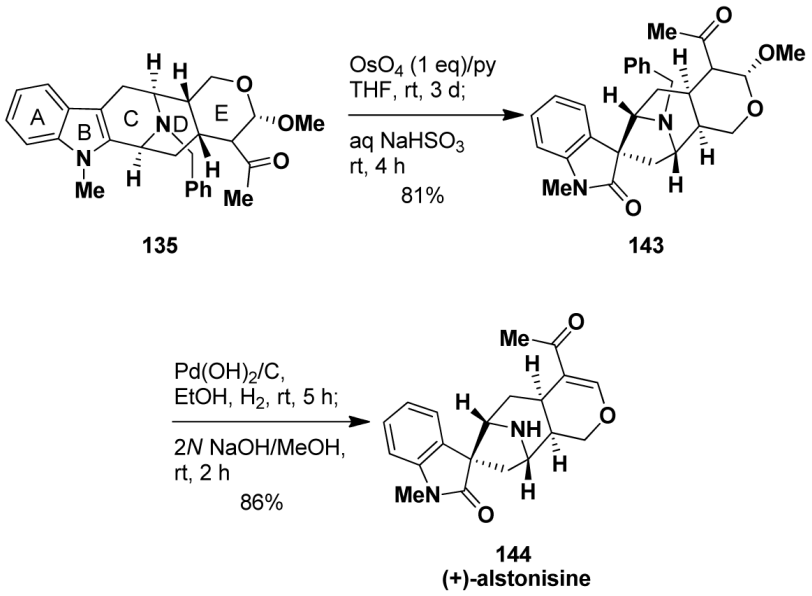
Aldehyde **145** was subjected to a Henry reaction with lithiated nitromethane, which furnished secondary alcohol **146** in 70% yield. This intermediate was then treated with Boc_2O in the presence of 4-*N*,*N*-dimethylaminopyridine (DMAP) to deliver isoxazoline **149** via a sequence consisting



Scheme 26. Diastereospecific formation of the oxindole moiety with OsO_4.

of alcohol activation, elimination, dehydrative formation of a nitrile oxide, and intramolecular dipolar cycloaddition.

Epoxidation of the enol ether **149** using dimethyldioxirane (DMDO) produced an unstable epoxide intermediate, which was immediately subjected to nucleophilic opening by [(1-ethoxyvinyl)oxy]trimethylsilane, under Lewis acid catalysis to furnish alcohol **150** in 56% yield. Although the epoxidation proceeded to give a 2:1 mixture of epoxide diastereomers in favor of the desired epoxide isomer, careful tuning of the reaction conditions permitted differential opening of only the major epoxide, with the minor diastereomer remaining unreactive. With isoxazoline **150** in hand, introduction of an alkyne

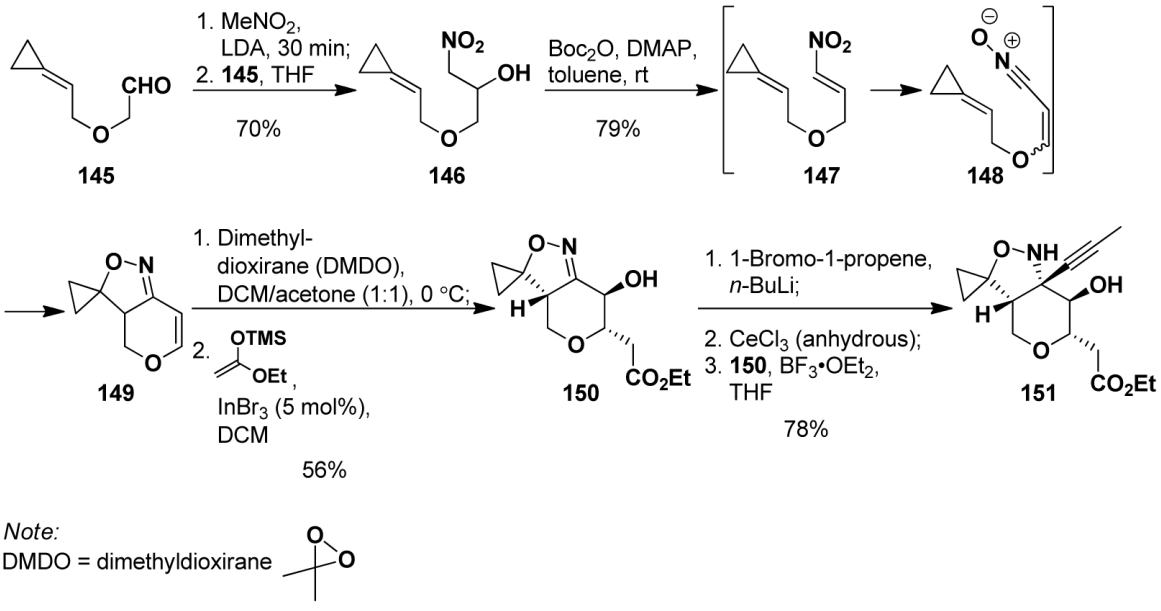


Scheme 27. Synthesis of alstonisine **144**.

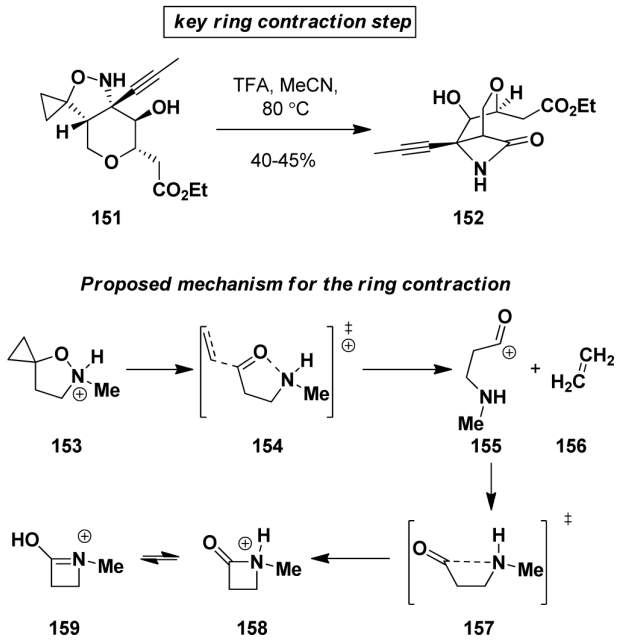
moiety was subsequently addressed. Accordingly, addition of 1-propynyllithium to **150** in the presence of anhydrous $CeCl_3$ and $BF_3{\cdot}OEt_2$ furnished diastereomerically pure oxazolidine **151** in 78% yield. Interestingly, the free secondary alcohol in **150** proved essential for the addition to proceed. It was speculated that the hydroxyl group was involved as a directing group for the incoming organometallic species.

With a route to spirocyclopropane isoxazolidine **151** secured, the key ring contraction to the projected β-lactam was then addressed by Diethelm et al, as shown in Scheme 29. Therefore, when **151** was treated with TFA at 80°C, the system underwent ring contraction to yield the highly substituted β-lactam **152** in 40%–45% after complete consumption of isoxazolidine **151**. The structure of β-lactam **152** was unambiguously confirmed by X-ray crystallographic analysis. Carreira et al recently proposed a mechanism for the ring contraction of spirocyclopropane isoxazolidines to form β-lactams based on experimental and computational studies (Scheme 29).[24]

The next hurdle in this synthetic effort was the methenylation of β-lactam **152** (Scheme 30). To this end, amide **152** was first protected using Boc_2O to furnish the corresponding imide in 85% yield. Exposure of this substrate to Petasis' olefination conditions led to clean conversion to strained enecarbamate **158**,[25] obtained in 77% yield. The stereocenter at C-5 was then



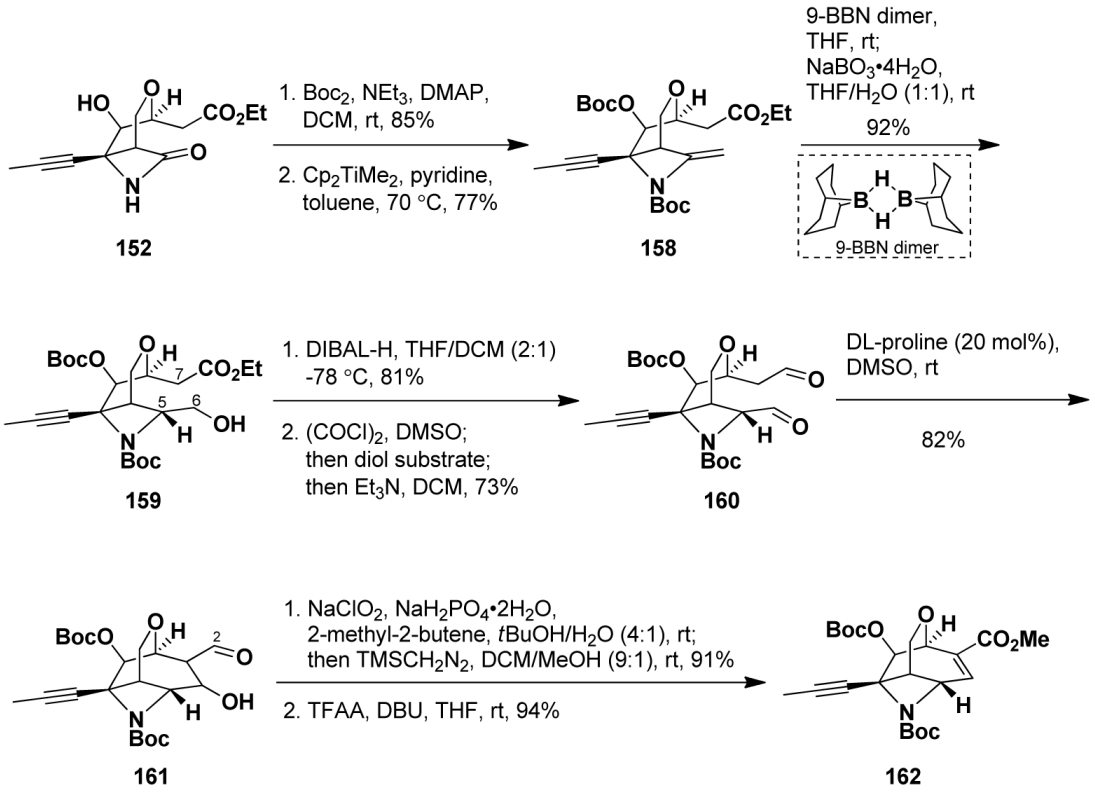
Scheme 28. Synthesis of intermediate **151**.



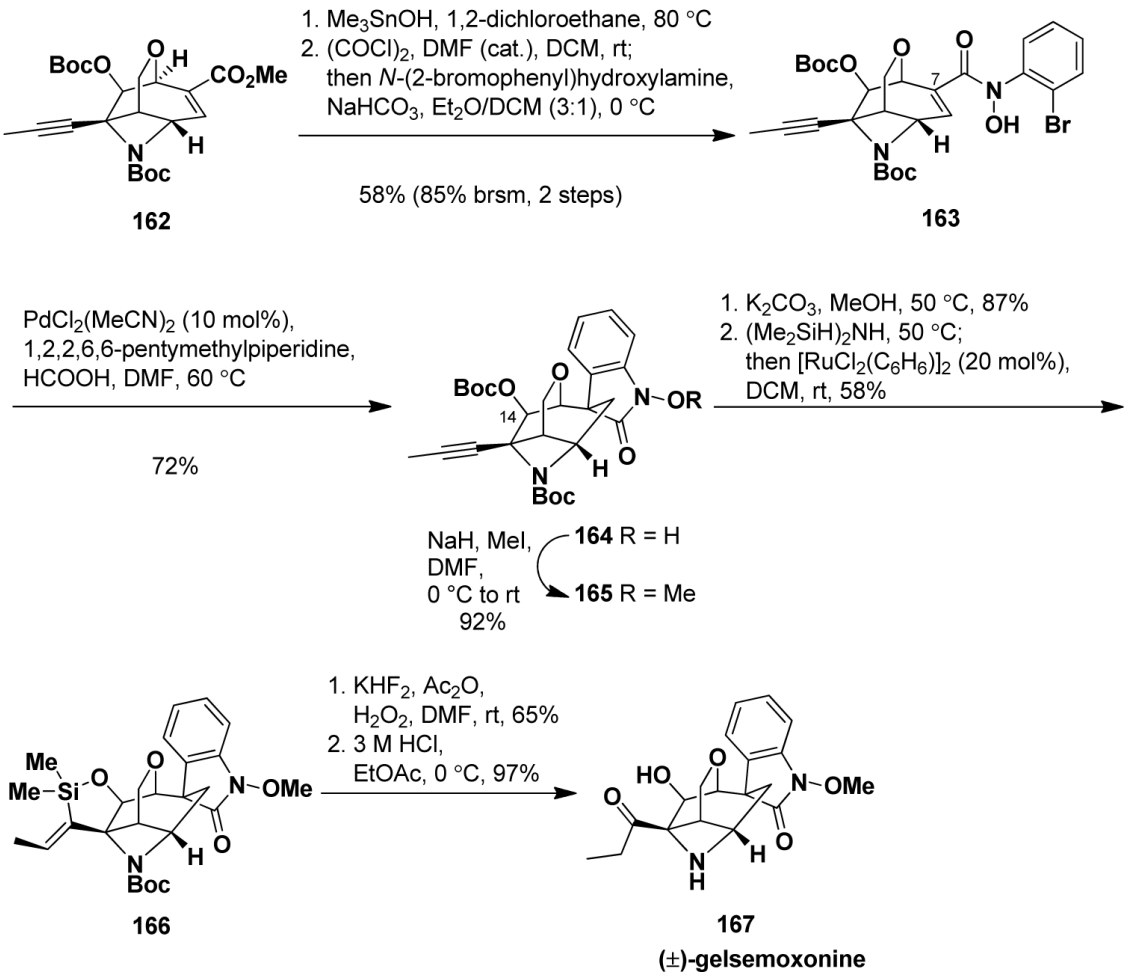
Scheme 29. Key ring contraction step.

installed by a hydroboration reaction. In this transformation, it was observed that the strained olefin in **158** reacted exclusively from the *exo*-face. Thus, following oxidative workup ($NaBO_3$), primary alcohol **159** was obtained in 92% yield as a single diastereomer. With the full carbon backbone of the gelsemoxonine core in place, closure of the seven-membered carbocycle was pursued. It was decided to explore an aldol condensation approach to achieve the requisite ring closure. To this end, dialdehyde **160** was prepared by DIBAL reduction of **159,** followed by oxidation of the intermediate diol under Swern conditions. When dialdehyde **160** was treated with 20 mol% of proline, aldol product **161** was isolated as a single diastereomer in 82% yield. Notably, no elimination of the secondary alcohol was observed under these conditions. Next, a sequence consisting of Pinnick oxidation/esterification in the presence of a free secondary alcohol delivered the corresponding methyl ester in 91% yield. Finally, elimination of the alcohol using TFAA furnished unsaturated ester **162** in 94% yield (Scheme 30).

With the tricyclic scaffold of gelsemoxonine in hand, Carreira et al focused on the introduction of the spirofused oxindole at C-7 (Scheme 31). Attention turned to the intramolecular addition of arylnucleophiles to the α,β-unsaturated carbonyl in **162**. Consequently, an intramolecular reductive Heck reaction offered an attractive approach to achieve such a transformation. Although the Heck reaction had been commonly used for the construction of quaternary stereocenters, including oxindole ring systems, the desired reductive variant of this transformation posed a few challenges when applied to the projected enone substrate **163**. Given that a putative aryl-palladium intermediate would be regiospecifically required to add to the congested C-7 carbon atom, the stereochemical outcome could not be predicted on steric grounds.



Scheme 30. Synthesis of unsaturated ester **162**.



Scheme 31. Synthesis of gelsemoxonine **167**.

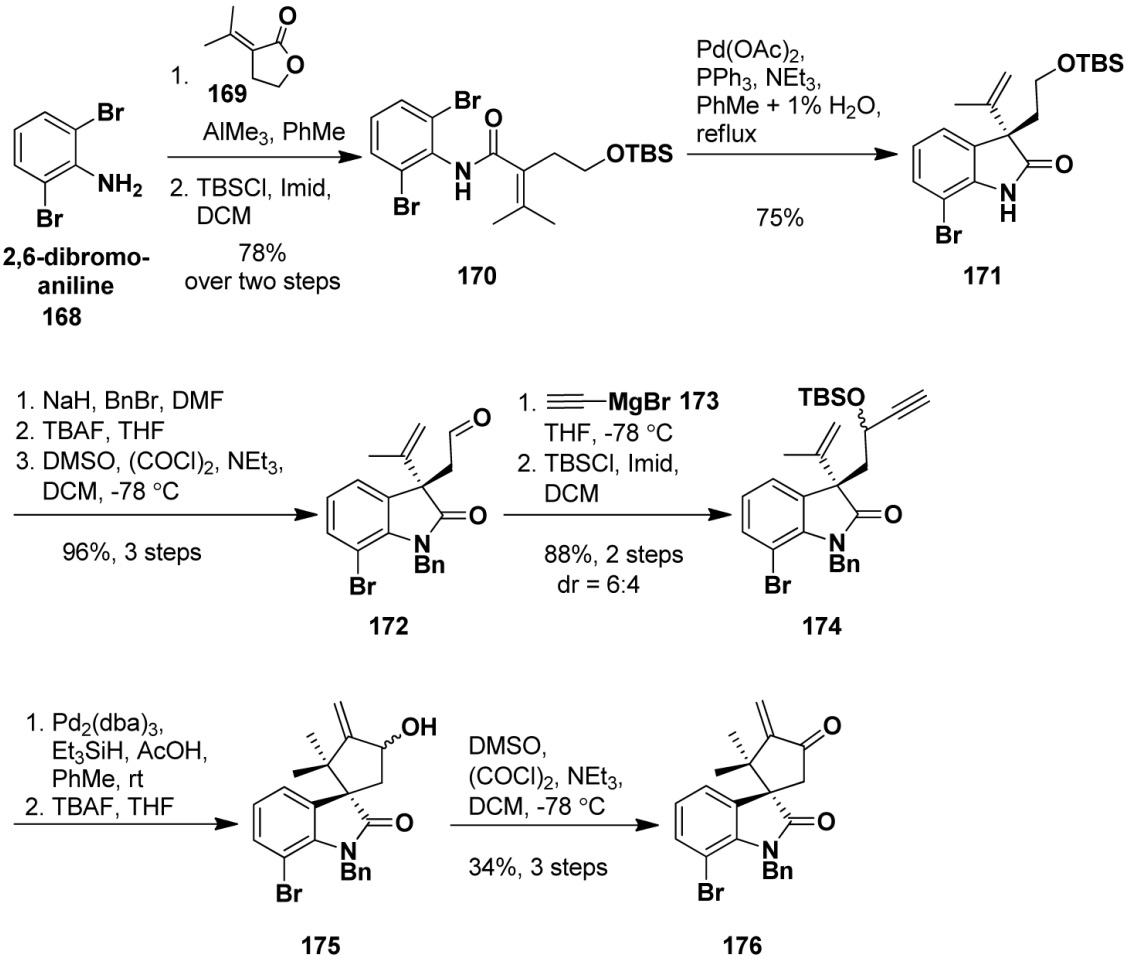
Additionally, reductive quenching of the resulting alkyl-palladium species could be complicated by various undesired competing side reactions. These included reopening of the oxindole ring, β-hydride elimination, side reactions involving the adjacent azetidine ring, and a potential cleavage of the N-O bond in **163**. In order to test the strategy, hydroxamic acid **163** was prepared following hydrolysis of ester **162** using Me_3SnOH. The carboxylic acid that resulted was then converted to the acid chloride and coupled to *N*-(2-bromophenyl) hydroxylamine.

Upon exposure of the aryl bromide **163** to reductive Heck conditions employed by Trost et al,[26] which used formic acid as the reductant, the formation of oxindole **164** was observed in 72% yield and as a single diastereoisomer. The *N*-hydroxyoxindole **165** was then methylated to deliver *N*-methoxy oxindole **165** in 92% yield. With the introduction of the oxindole secured, installation of the ethyl ketone remained as the final task in the synthetic route.

To this end, a protocol that involved hydroxyl-directed hydrosilylation of the triple bond was employed. Following this strategy, the C-14 Boc-carbonate was selectively cleaved using K_2CO_3 in MeOH in 87% yield. The secondary alcohol, which resulted, was subjected to hydrosilylation conditions, employing $[RuCl_2(C_6H_6)]_2$ as a catalyst to furnish the vinylsilane **166** in 58% yield as an inconsequential mixture of olefinic isomers. Oxidation of this mixture under Tamao–Fleming conditions delivered ethyl ketone in 65% yield.[27] The removal of the *N*-Boc carbamate using 3 M HCl delivered the natural product (±)-gelsemoxonine **167** in 97% yield.

3.2 Wood et al's enantioselective total synthesis of (+)-citrinadin B. In 2013, Wood et al reported an enantioselective synthesis of the naturally occurring alkaloid (+)-citrinadin B **191**. The synthetic effort revealed an anomaly in the original structural assignment that has led to a stereochemical revision. The reported synthesis was convergent and employed a stereoselective intermolecular nitrone cyloaddition reaction as the key step.[28]

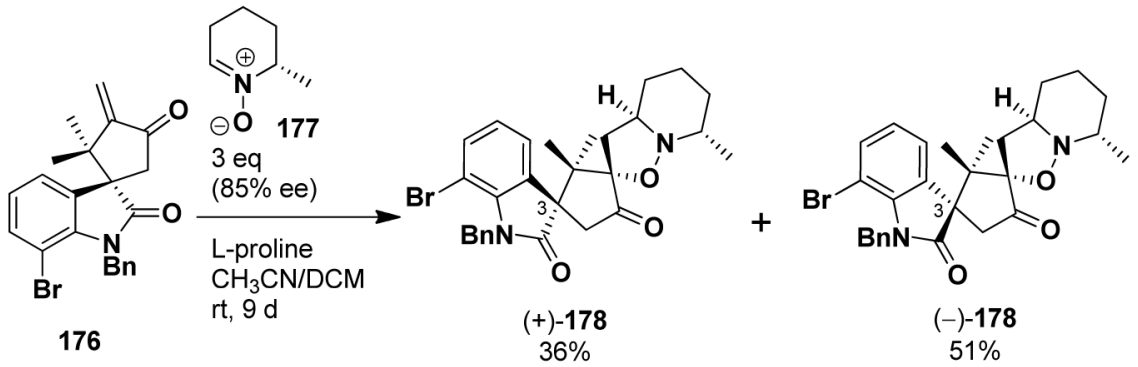
The synthesis began with the exposure of 2,6- dibromoaniline **168** to trimethylaluminum, followed by lactone **169**, which furnished an intermediate alcohol that was protected as the corresponding silyl ether **170** (Scheme 32). Cyclization of the amide **170** to oxindole (±)-**171** under Heck conditions was



Scheme 32. Synthesis of intermediate **176**.

followed by benzyl protection, silyl group cleavage, and alcohol oxidation to furnish aldehyde (±)-**172**. At this point, the stage was begun to be set for an eventual reductive eneyne cyclization by treating oxindole (±)-**172** with ethynyl Grignard. Addition of the Grignard was immediately followed by protection of the resulting diastereomeric alcohols as their corresponding silyl ethers (±)-**174**. Cyclization of (±)-**174** was then accomplished under conditions developed by Trost and Rise,[29] which was then followed by a TBAF-mediated deprotection process to afford a diastereomeric mixture of alcohols (±)-**175**. Oxidation of the latter under Swern conditions provided the dipolar cycloaddition substrate, enone (±)-**176** (Scheme 32).

With both enone (±)-**176** and nitrone (–)-**177** in hand, Chackalamannil and Wang explored the critical [3 + 2] cycloaddition (Scheme 33).[30] It was found, under various conditions, that only two diastereomeric cycloaddition products, (+)-**178**



Scheme 33. Syntheis of intermediate **178**.

and (–)-**178**, were observed. After considerable experimentation, the addition of L-proline to this reaction had a beneficial effect on both the rate and the observed diastereomeric ratio.

Extensive studies into the resultant stereochemistry revealed that cycloadducts (+)-(**178**) and (–)-(**178**) differed only by their configuration at the spirooxindole center at C-3. Moreover, the relative stereochemistry resident in the minor product (+)-**178** was that required for the conversion to the natural product.

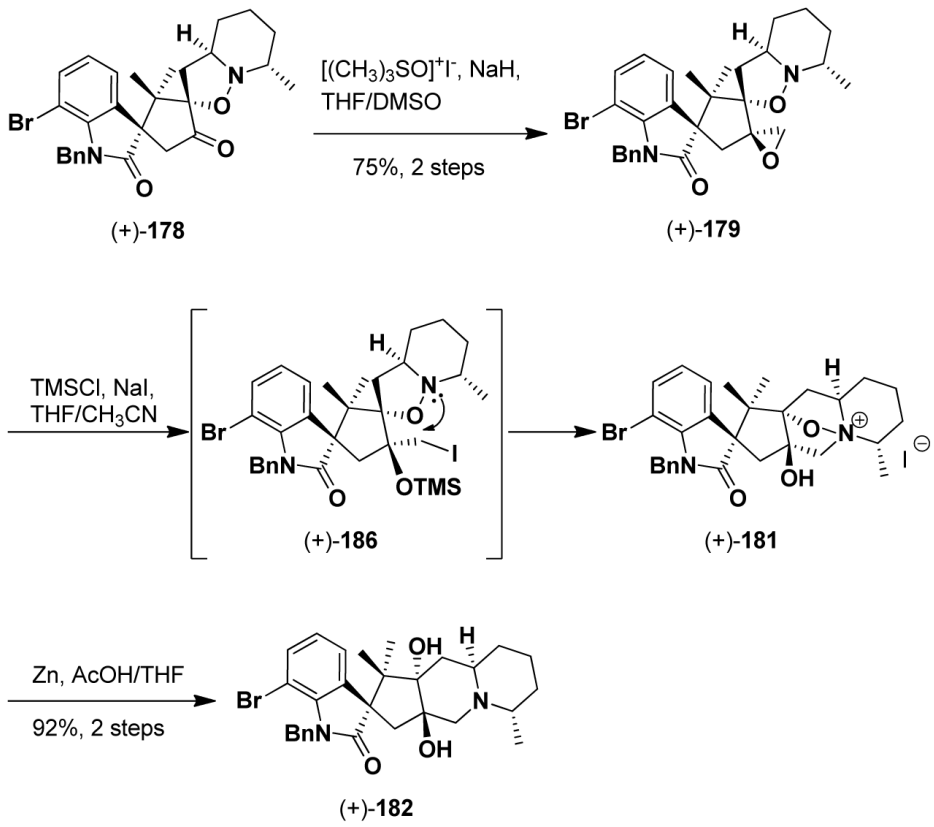
Completion of the natural product by this approach required the addition of a carbon atom, as well as closure of the central-fused D-ring of the citrinadin core. In order to address both of these concerns, it was reasoned that a Corey–Chaykovsky epoxidation would permit introduction of a single-carbon atom and set the stage for subsequent ring closure via an intramolecular nucleophilic attack of the proximal nitrogen atom onto the derived epoxide. In any event, exposure of oxindole (+)-**178** to dimethylsulfoxonium methylide furnished the corresponding spiroepoxide (+)-**179** as a single diastereomer (Scheme 34). Although initial attempts to promote intramolecular opening of the epoxide were unsuccessful, eventually it was found that exposure of epoxide (+)-**179** to TMSI generated in situ furnished ammonium salt (+)-**181** in good yield, presumably, via the intermediacy of iodide **186**. The ammonium salt (+)-**181** proved to be an excellent substrate for a Zn-mediated N-O bond cleavage reaction that delivered diol (+)-**182**.

Then, diol (+)-**182** was converted to the corresponding epoxide (+)-**184**, which was subsequently coupled with 3-methyl-1-butyne under Sonogashira conditions to give alkyne (+)-**185** (Scheme 35). Importantly, the alkyne moiety in the derived product (+)-**185** proved very resistant to the harsh benzyl deprotection conditions, but tolerated a subsequent epoxide-opening reaction with $MgCl_2/NaN_3$ to furnish azide (+)-**186**. Thereafter, exposure of azide (+)-**186** to the gold-mediated oxidation conditions reported by Lu et al permitted conversion of the alkyne moiety to an enone, thereby delivering azido alcohol (+)-**188** (Scheme 35).[31]

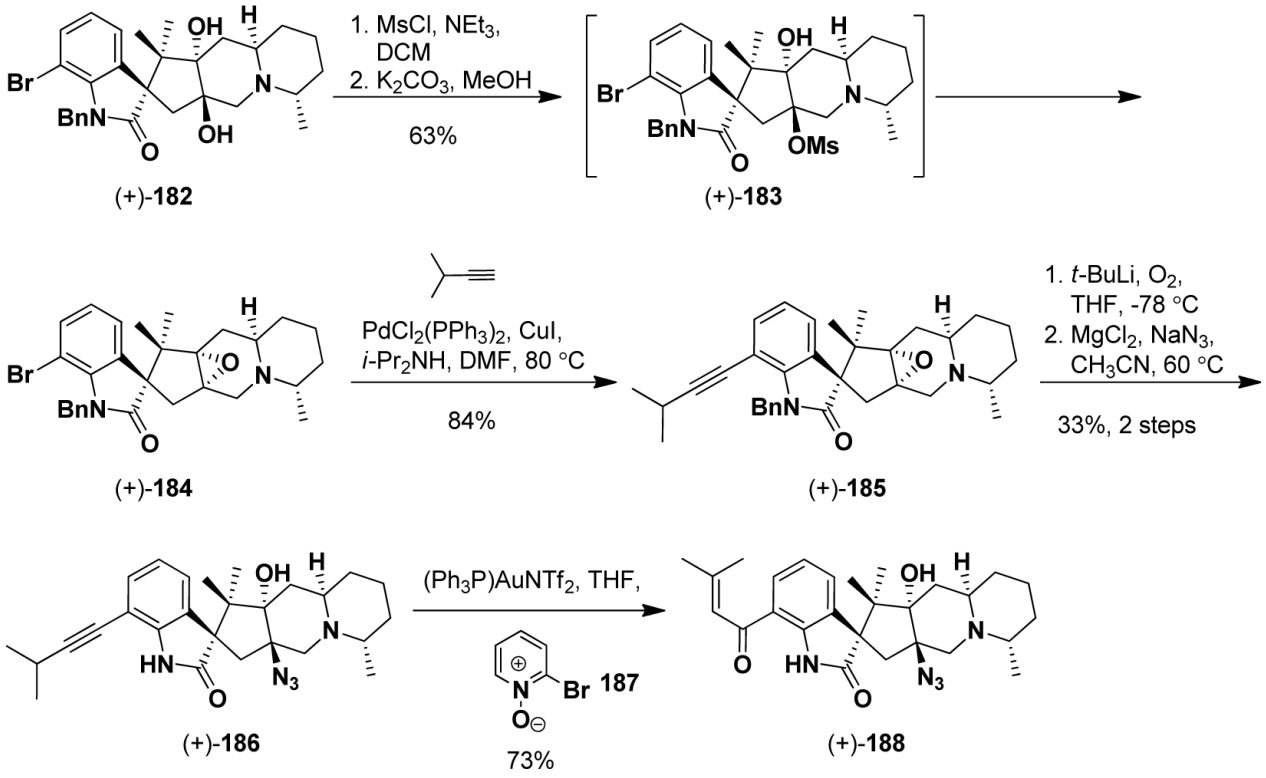
Next, a diastereoselective enone epoxidation was selected to complete citrinadin B **191**, and a protocol developed by Enders et al proved most effective [the ratio of epoxide diastereomers could be increased in favor of (–)-**190** when (*S,S*)-*N*-methylpseudoephedrine **189** was used as an additive], as shown in Scheme 36.[32] Pentacyclic epoxide (–)-**190** was advanced through the sequence of azide reduction, monomethylation, and deprotection, to furnish the target (+)-citrinadin B **191** in 68% over the last three steps.

3.3 Martin et al's enantioselective total synthesis of citrinadins A and B.

3.3.1 Total synthesis of (–)-citrinadin A. Simultaneous with the report of Wood et al, Martin et al disclosed the first total synthesis of (–)-citrinadin A **216** by a linear approach, in which the first chiral center was created by an enantioselective

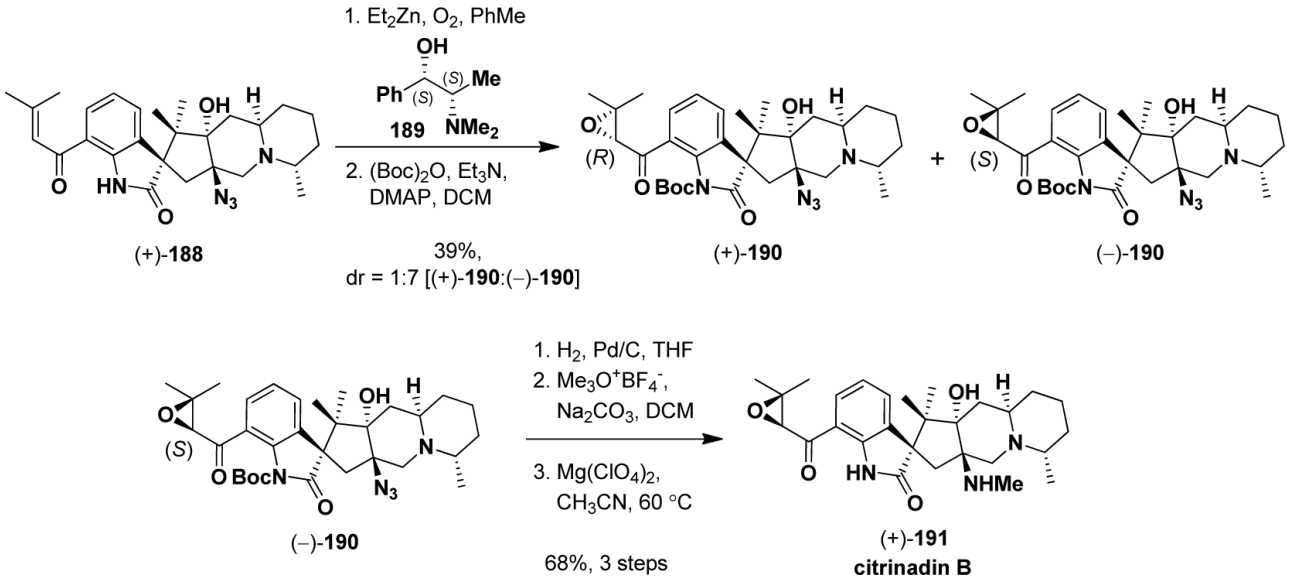


Scheme 34. Synthesis of pentacyclic oxindole **182**.

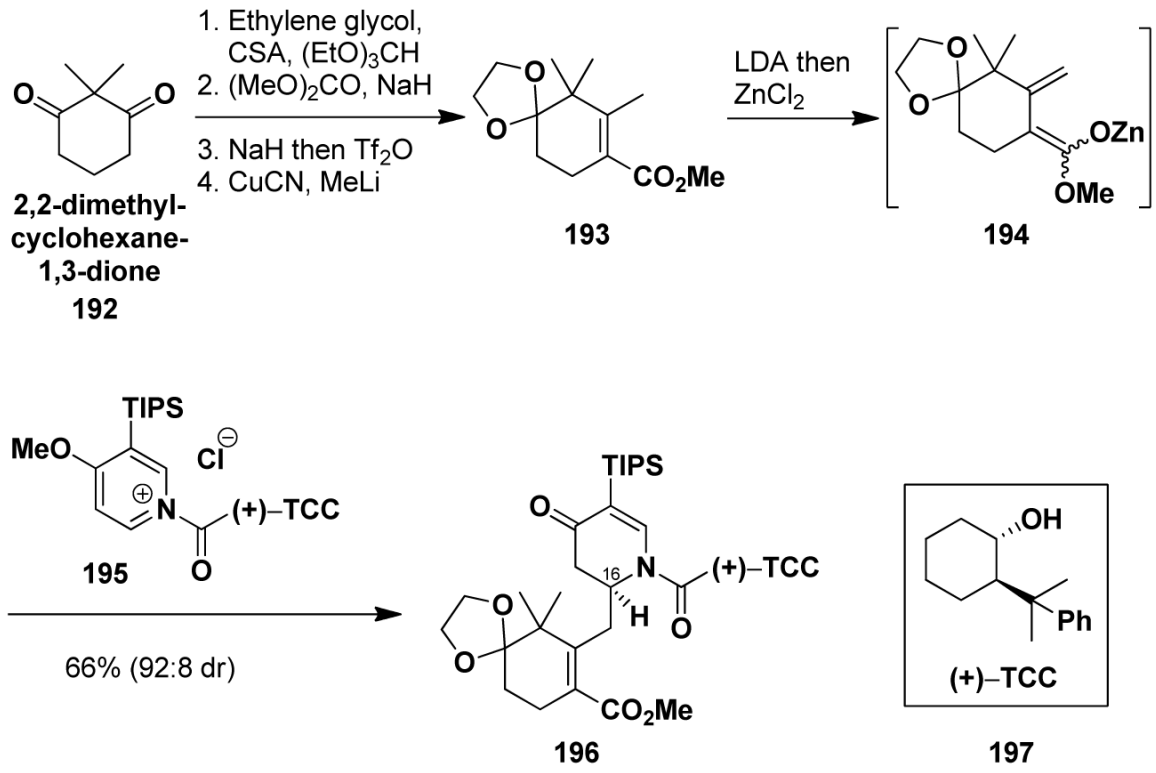


Scheme 35. Synthesis of pentacyclic enone **188**.

vinylogous Mannich addition, and the remaining stereocenters on the pentacyclic core were set by substrate-based control.[33] The synthetic route began from commercially available 2,2-dimethylcyclohexane-1,3-dione, which was transformed into the α,β-unsaturated ester **193** in four straightforward steps that involved protection, crossed Claisen condensation, enol triflate formation, and methylation (Scheme 37). Deprotonation of ester **193** with LDA, followed by transmetalation with $ZnCl_2$, gave the vinyloxy zinc adduct **194**. After this success, the stereoselectivity of the addition of the zinc dienolate **194** to the chiral pyridinium salt **195** was examined. The salt **195** was generated in situ by the reaction of 3-TIPS-4-methoxypyridine and the chloroformate derivative of (+)-*trans*-2-(α-cumyl)-cyclohexanol [(+)-TCC], as shown in



Scheme 36. Synthesis of citrinadin B **191**.



Scheme 37. Synthesis of intermediate **196**.

Scheme 37. This reaction proceeded successfully to give **196** with high diastereoselectivity (dr = 92:8), and the required absolute stereochemistry at the newly created stereocenter at C-16 was verified by X-ray crystallography of a derived intermediate.

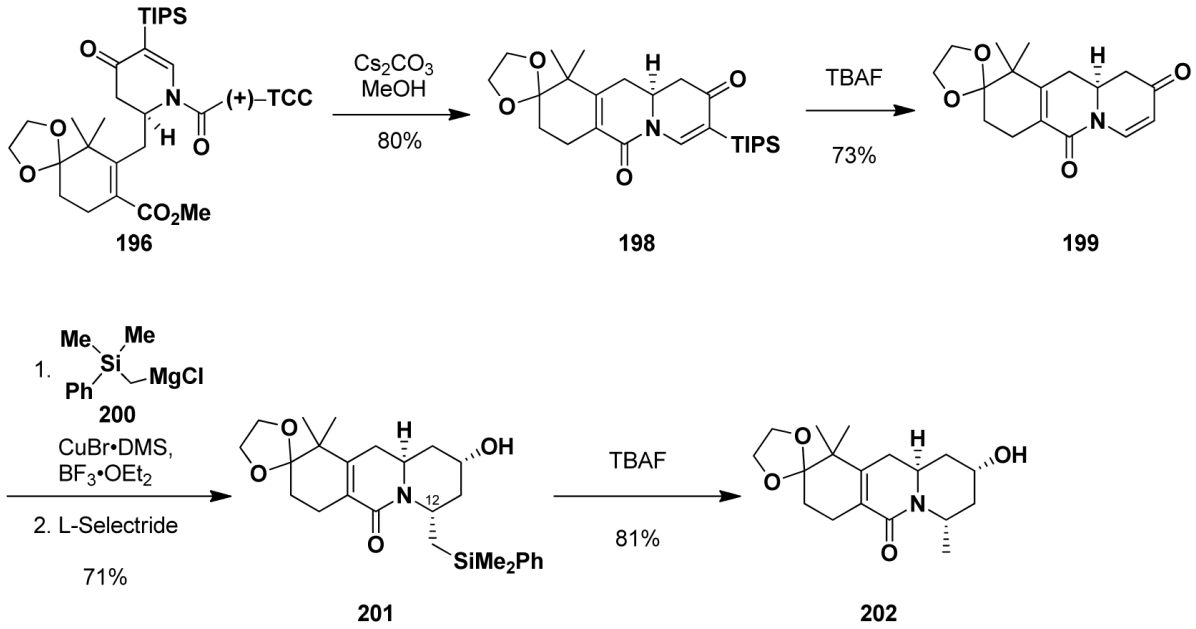
Exposure of **196** to Cs_2CO_3 in methanol induced removal of the (+)-TCC chiral auxiliary, and spontaneous cyclization ensued to provide the lactam **198** in 84% ee (improved to 99% ee after crystallization) together with about 70% recovered (+)-TCC. The desilylation of the lactam **198** was most efficiently effected employing excess TBAF and microwave-mediated heating to afford enone **199**.

Martin et al discovered that the organocopper reagent generated from (dimethylphenylsilyl)-methylmagnesium chloride and CuBr·DMS added smoothly to enone **199** in the presence of $BF_3{\cdot}OEt_2$ to give a mixture of ketones that were directly reduced using L-selectride with high stereoselectivity to give **201** in 71% yield over two steps; 19% of the C-12 epimer of **201** was also isolated. Alcohol **201** was then heated with TBAF in a microwave oven to obtain the unsaturated lactam **202** (Scheme 38).

The transformation of enantiomerically pure **202** into **205** was straightforward. Epoxidation of **202** with peroxytrifluoroacetic acid in the presence of sodium carbonate was highly diastereoselective, proceeding from the more accessible, slightly convex face to furnish a single epoxide **203** (Scheme 39). The reaction of epoxide **203** with aqueous methylamine in a sealed tube also occurred with high diastereoselectivity to deliver the requisite amino alcohol **204** in 95% yield. The heating of ketal **204** with *o*-bromophenylhydrazine hydrochloride in aqueous sulfuric acid provided the indole **205** in 81% yield (Scheme 39). The Fischer indole reaction could only occur regiospecifically to provide the 7-bromoindole **205**.

In the last stages of the synthetic route, enantiomerically pure pentacyclic indole **205** was readily transformed into enantiomerically pure oxindole **208** (Scheme 40). The reduction of the lactam **205** with the complex of alane and dimethylethylamine (DMEA) delivered reduced indole **206** in excellent yield. Subsequent treatment of indole **206** sequentially with pyridinium *p*-toluenesulfonate (PPTS), with excess of Davis's oxaziridine **207**, and then with acetic acid provided the spirooxindole **208** as a single stereoisomer (the unique role that PPTS played in controlling the stereochemical outcome of this reaction was not understood yet).

Then, Martin et al[33] turned to a stepwise procedure that began with the Sonogashira coupling between oxindole **208** and 3-methylbut-1-yne to furnish the alkyne **210**. Regiospecific acylation of the secondary hydroxyl group at C-14 with *N*,*N*-dimethyl-l-valine in the presence of 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide (EDCI) and DMAP provided oxindole ester **212** in excellent yield. According to a method reported by Lu et al, the gold-promoted oxidation of alkyne **212** using 2-bromopyridine *N*-oxide gave the enone **214**.[31] Finally, diastereoselective epoxidation of enone **214** to deliver a mixture (5:1) of epoxides (–)-citrinadin A **216** and

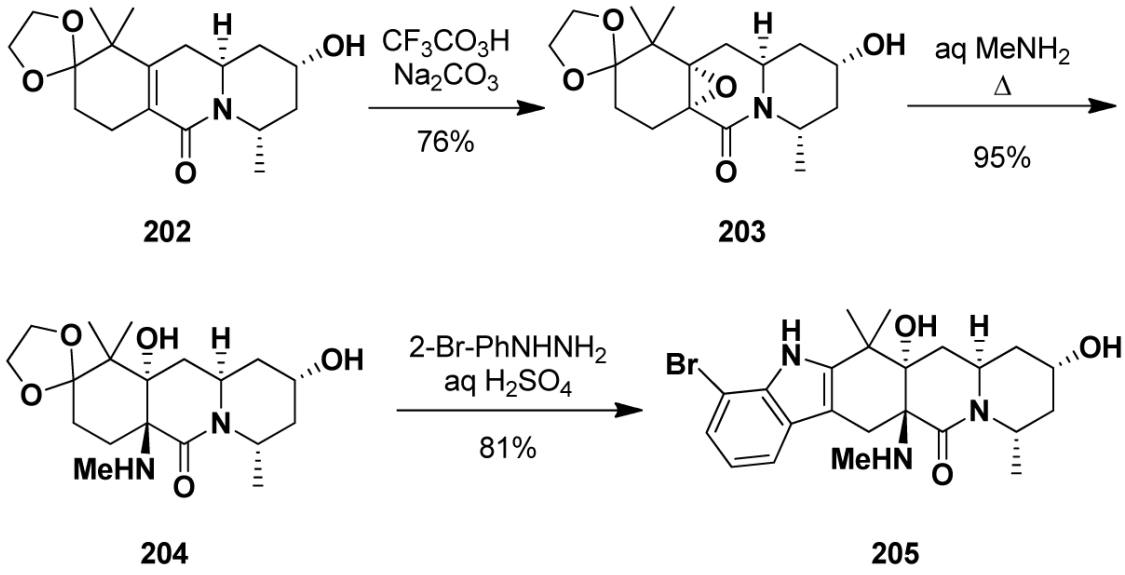


Scheme 38. Synthesis of tetracyclic intermediate **202**.

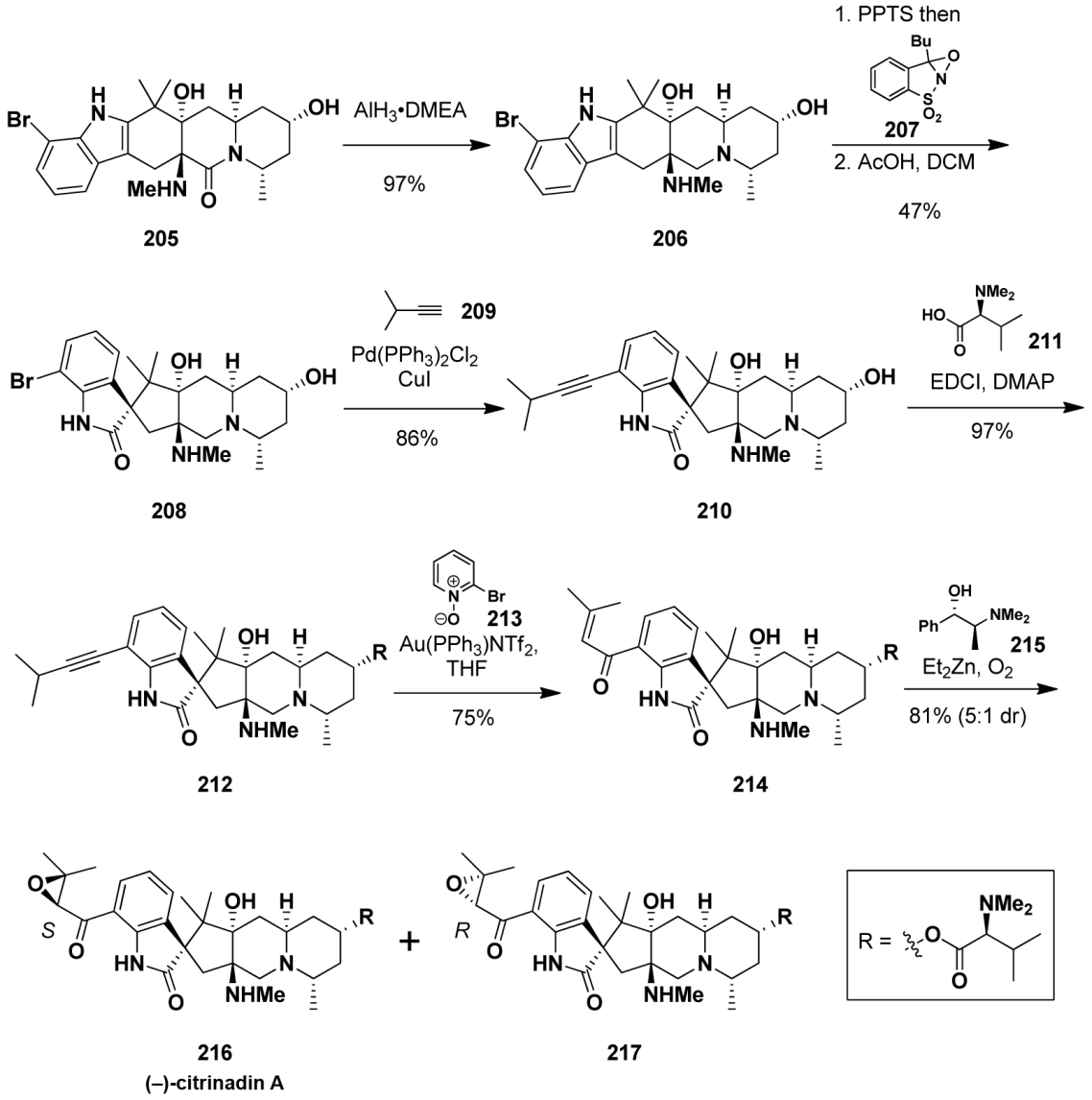
217, respectively, was achieved by applying an Enders protocol for the enantioselective synthesis of (*S*)-epoxides from α,β-unsaturated ketones using (*S,S*)-*N*-methylpseudoephedrine as the chiral ligand.

3.3.2 Total synthesis of (+)-citrinadin B. The difference between citrinadin A **216** and citrinadin B **191** is the presence of a dimethyl valine ester at C-14. Accordingly, it could be envisaged that deoxygenation at C-14 of a late-stage intermediate in the synthesis of citrinadin A 216 would give a precursor of citrinadin B **191**. Thus, Barton's deoxygenation of alcohol **202** afforded lactam **218** in 73% yield (Scheme 41).

Epoxidation of the α,β-unsaturated lactam **218** using buffered peroxytrifluoroacetic acid gave epoxide **219** (77% yield) as a single stereoisomer when **219** was heated with aqueous methylamine, the desired amino alcohol **220** was isolated in 94% yield. The Fischer indole reaction of acetal **220** with *o*-bromophenylhydrazine hydrochloride furnished the pentacyclic indole **221**, which was then converted to the spirooxindole **223** in 34% overall yield by sequential hydride reduction of the tertiary lactam, indole oxidation with Davis' oxaziridine **222**, and acid-catalyzed rearrangement of the intermediate epoxide. The aryl bromide moiety of **223** was then elaborated



Scheme 39. Synthesis of pentacyclic indole **205**.

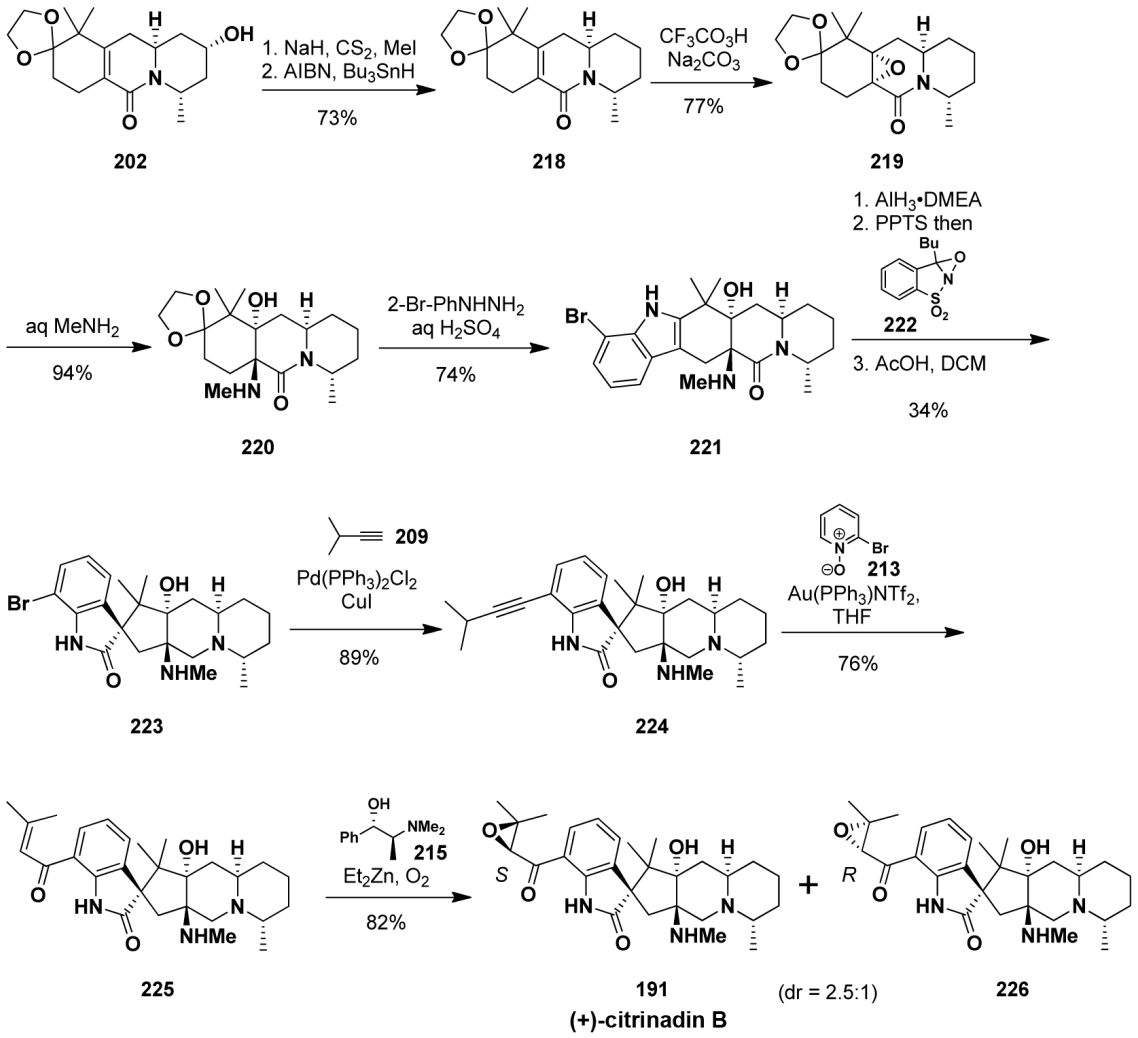


Scheme 40. Synthesis of (–)-citrinadin A **216**.

via a Sonogashira coupling with 3-methylbut-1-yne to furnish the alkyne **224** that was processed to the enone **225** in 68% overall yield from **223** by reaction with 2-bromopyridine *N*-oxide in the presence of gold. Finally, epoxidation of enone **225** using the Enders procedure afforded a separable mixture of (+)-citrinadin (B) **191** and the (*R*)-diastereomer **226** (**191**/**226** = 2.5:1 dr).[32]

3.4 Sarpong et al's enantioselective total synthesis of the *ent*-citrinadin B and cyclopiamine B.[34–44] Sarpong et al initiated their synthetic studies toward the total synthesis of *ent*-citrinadin B and cyclopiamine B with the protection of D-proline **227** by a Boc group (Scheme 42), which was followed by the reduction of the carboxylic acid group and Swern oxidation of the resulting hydroxyl moiety to afford the aldehyde **228**.[34] Alkynylative homologation of the aldehyde group of **228** using the Ohira–Bestmann method,[34] followed by removal of the *tert*-butoxycarbonyl group and acylation with 2-cyanoacetyl chloride, gave alkyne **229**. This served as a substrate for an unprecedented formal cycloisomerization that probably proceeds via a metal vinylidene intermediate,[35] anti-Markovnikov hydration, and Knoevenagel condensation to give tetrahydroindolizinone **230**. At this stage, a $SnCl_4$-catalyzed Diels–Alder reaction between **230** and diene **231**,[36] and a subsequent basic workup, afforded an enone (not shown), which was iodinated to yield iodoenone **232** (Scheme 42).[37]

The hydrolysis of the nitrile group of **232** was achieved using a Pt-complex **233** to afford the corresponding carboxamide,[38] which served as a substrate for a Hofmann rearrangement that was effected with phenyliodosyl bistrifluoroacetate to yield carbamate **234**.[39] The Suzuki cross-coupling of **234** with the known boronic ester **235** gave adduct **236**,[40] which was efficiently converted to the fused indole **237** using two

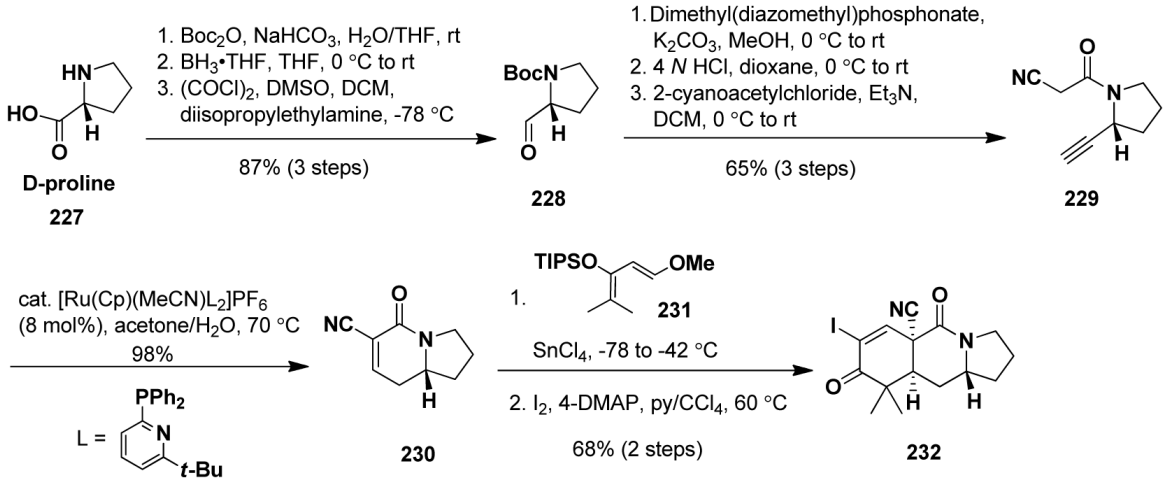


Scheme 41. Synthesis of citrinadin B **191**.

sequential reductions, all in accord with the effective protocols established in the literature (Scheme 43).[41]

At this stage, Sarpong et al opted to effect a Wacker oxidation of the chromene ring of **237** to afford chromanone **238** (Scheme 44), which was advantageous because the chromanone unit is not found in the citrinadins and cyclopiamines. Importantly, treatment of **239** (following removal of the methoxycarbonyl group in **238**) with an excess of DMDO (formed in situ from acetone and Oxone) afforded spirooxindole **240** as the major product (4:1 dr), where in the spirocenter was as desired and the nitro group was installed in one pot. Studies of DMDO oxidations of indoles to spirooxindoles suggested that spirooxindole **240** might arise from epoxide A **243** (Scheme 44).[42] Therefore, it was possible that the introduction of the chromanone diminished the participatory role of the indole nitrogen lone pair leading, after rearrangement to **240**. With spirooxindole **240** in hand, what remained was a selective removal of the tertiary amide carbonyl group by reduction, which had to be accomplished in the presence of the chromanone and secondary amide carbonyl groups as well as the newly introduced nitro group. After extensive investigation by Sarpong et al, this task was effectively accomplished using a modification of a known procedure by treating oxindole **240** with a variant of Meerwein's salt ($Me_3O{\cdot}BF_4$),[43] which probably leads to a methylated amidinium intermediate that is cleanly reduced with sodium cyanoborohydride to give *ent*-citrinadin B **241** in 66% yield (79% based on the recovered starting material). *Ent*-citrinadin B **241** was easily converted to cyclopiamine B **242** on treatment of oxindole **241** with sodium hydride, followed by heating (to effect the conversion of chromanone to tetrahydroquinolone) and subsequent methylation of the phenol, which resulted to give the target oxindole **242** (Scheme 44).[44]

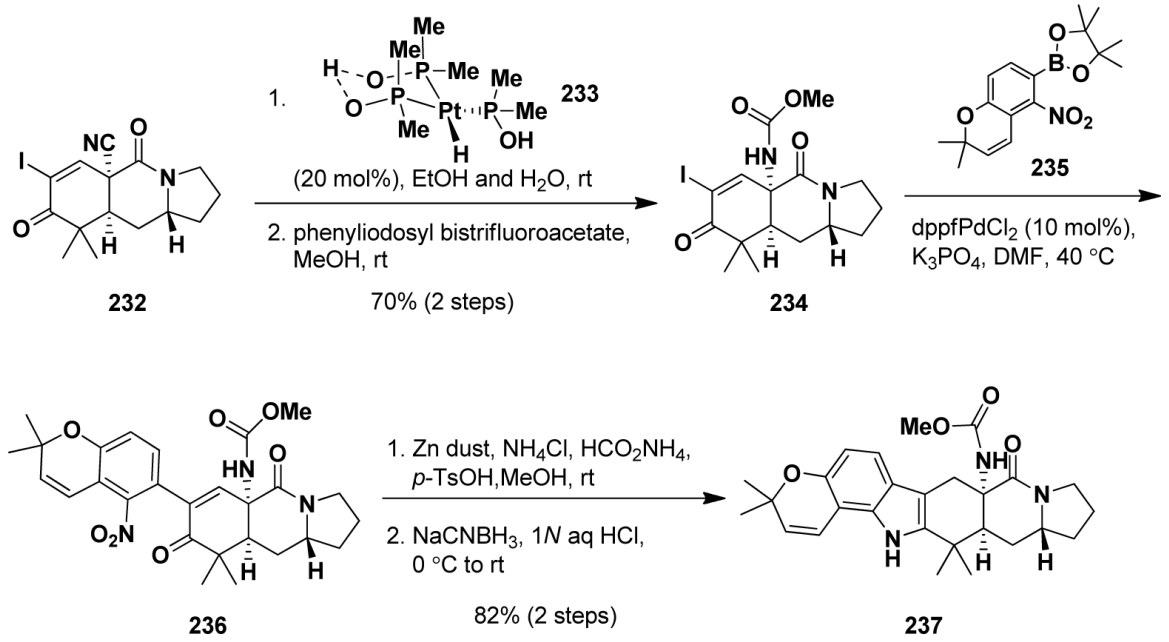
3.5 Qin et al's biomimetic total synthesis of (+)-gelsemine. Qin et al reported a biomimetic total synthesis of (+)-gelsemine **264**, in which the key reaction involved an intramolecular enol–oxonium cyclization that assembled the required cage structure in a highly efficient manner. In addition, a new biosynthetic pathway for the later stages of the biosynthesis of gelsemine was proposed based on



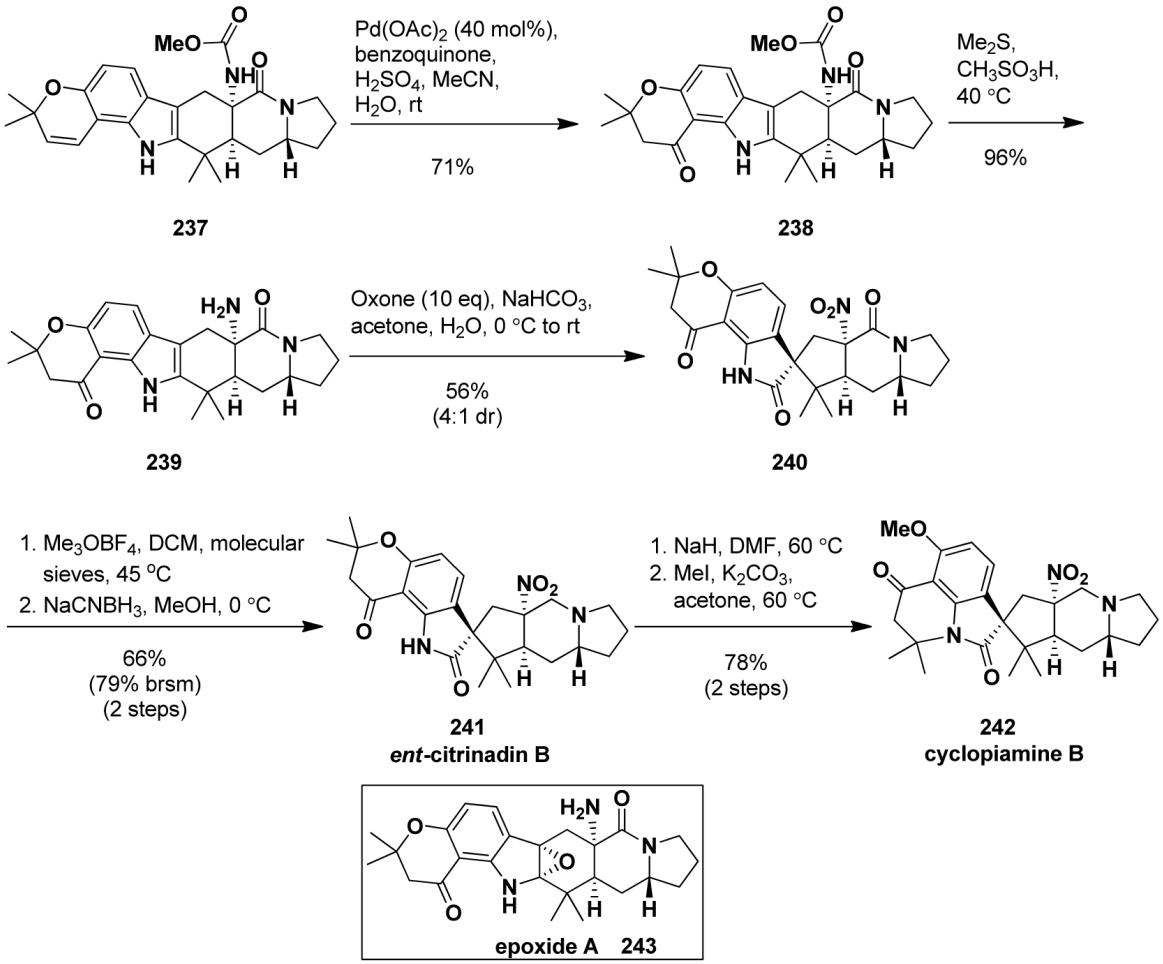
Scheme 42. Synthesis of intermediate **232**.

the enol–oxonium cyclization procedure executed during these studies.[45]

Qin et al began toward gelsemine **264** by converting disubstituted aziridine **243** to the chiral *cis* tetra-substituted piperidinoaldehyde **243** (Scheme 45).[45] Two steps of reduction and tosylation of **243** provided the alcohol (*R,R*)-**244** in moderate yield. The attack by (3,3-diethoxyprop-1-yn-1-yl)lithium on aziridine **244** occurred from the top face of the aziridine ring to afford alkyne diethylacetal **246** as a single stereoisomer in 95% yield. The excellent regio- and stereoselectivity was presumably due to coordination of the lithium reagent with the hydroxy group and efficient blockage of the bottom face of the aziridine ring by the bulky OTBDMS group in **244**. Subsequent N-methylation with MeI and protection of the hydroxy group in alkyne **246** provided acetal **247** in excellent yield. After removal of the tosyl group with Mg dust using ultrasound, the amine, which resulted, reacted with acrylonitrile in MeOH at reflux to provide alkyne-nitrile **248** in excellent yield. Subsequent treatment of nitrile **248** with TFA and oxidation of the resulting aldehydic group with sodium chlorite yielded acid **249** in 85% yield in two steps. The partial hydrogenation of the alkynyl group to an olefin with Lindlar catalyst and removal of the TBDMS group with HF/pyridine in **249** provided *cis*-olefin **250** in excellent yield. To prepare the piperidine ring with an (*S*)-configuration at C-15 as in the structure of (+)-gelsemine, an oxepinone ring was first



Scheme 43. Synthesis of fused indole **237**.



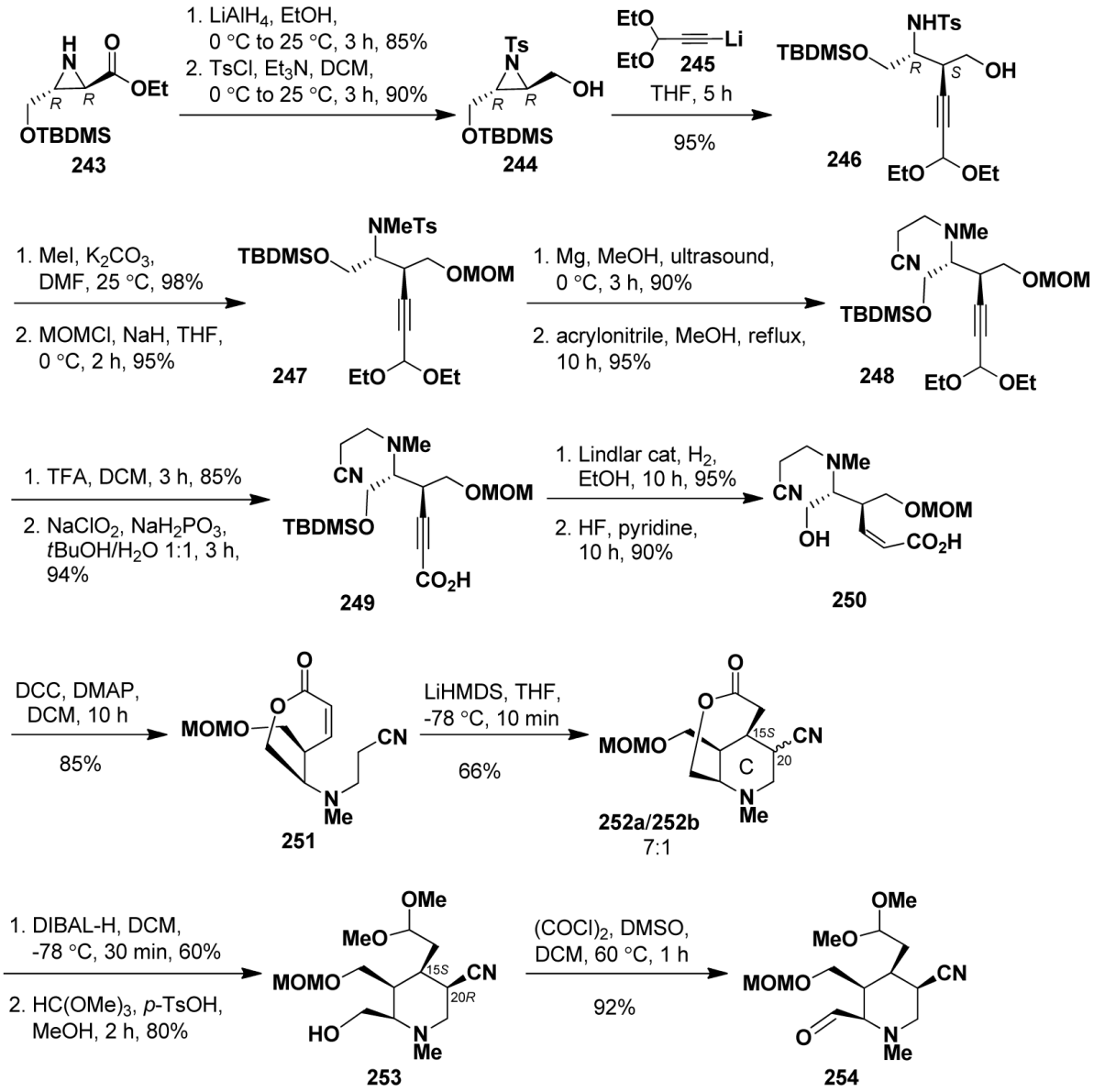
Scheme 44. Synthesis of *ent*-citrinadin B **241** and cyclopiamine B **242**.

generated by condensation of the acid group with the hydroxy group in **250** to give lactone **251** in 85% yield. Intramolecular Michael addition at low temperature yielded two inseparable diastereomers (15*S*,20*R*)-**252a** and (15*S*,20*S*)-**252b** in 66% yield in a 7:1 ratio. The latter mixture of diastereomers became separable after the lactone group was reduced to an aldehyde with DIBAL-H at low temperature, and the aldehydic group, which resulted, was protected with a dimethoxy acetal group, affording the major isomer of methylpiperidine (15*S*,20*R*)-**253** in 48% yield over two steps. The subsequent oxidation of the hydroxy group provided the *cis* tetra-substituted piperidinoaldehyde **254** in 92% yield (Scheme 45).

With the piperidine **254** bearing the required stereochemistry in hand, Qin et al began to prepare oxindole **259** (Scheme 46). The condensation of piperidine **254** with *N*-methoxyoxindole in the presence of LDA, followed by dehydration of the resulting hydroxy group with $SOCl_2$/pyridine, provided two separable geometric isomers (*Z*)-**256a** and (*E*)-**256b** in a 1.5:1 ratio. The isomeric mixture **256** easily underwent Michael addition in the presence of LDA in THF to yield two inseparable oxindole diastereomers **257** (epimeric at C-7 in 75% yield). The Michael addition of **256** not only formed the D-ring but also created the correct C-20 quaternary carbon center with an (*R*)-configuration. However, the addition led to an (*S*)-configuration at C-6 rather than the desired (*R*)-configuration. The (*S*)-configuration at C-6 prevented the oxindole moiety from gaining access to the oxonium cation that was formed in situ when the MOM group and the two methoxy groups in **257** were removed under acidic conditions. To invert the C-6 (*S*)-configuration in **257** to an (*R*)-configuration and thereby allow construction of the E- and F-rings by enol–oxonium cyclization, a double bond between C-6 and C-7 was generated to yield two separable geometric isomers **258a** and **258b** in 70% yield in a 5:1 ratio by using the standard protocol of olefination with PhSeCl/LDA/$NaIO_4$ (Scheme 46).

Hydrogenation of the double bond in the isomeric mixture **258** with Lindlar catalyst and hydrogen in MeOH resulted in two inseparable diastereomers **259a** and **259b** in 90% yield in a 2:1 ratio. The hydrogenation proceeded such that the nucleophilic attack occurred from the less hindered bottom face of the double bond, thereby yielding **259a** and **259b** with C-6 exclusively in the (*R*)-configuration.

Qin et al next carried out the planned one-pot, multistep enol–oxonium cyclization reaction cascade to efficiently



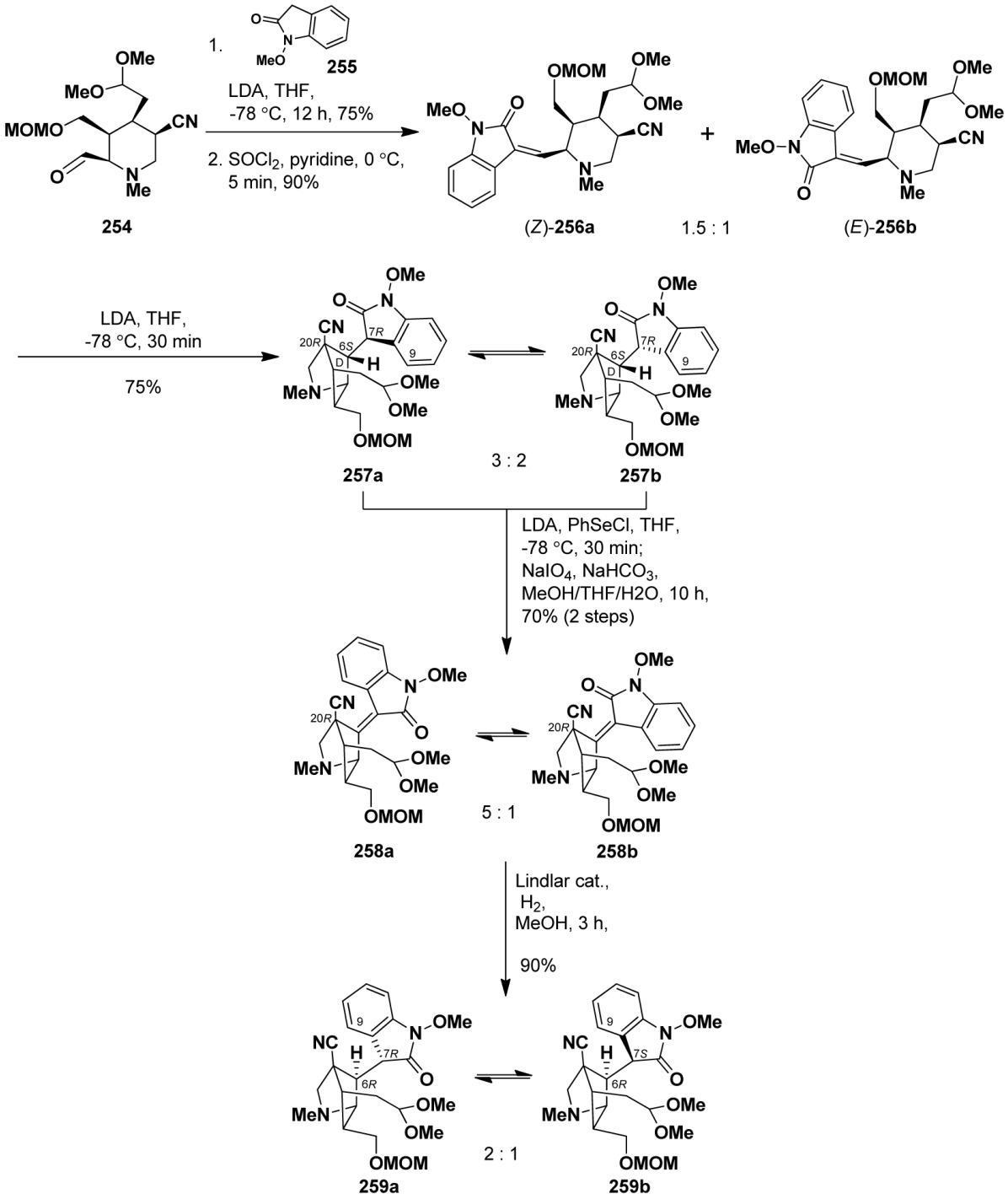
Scheme 45. Synthesis of methyl piperidine intermediate **254**.

assemble both the E- and F-rings and simultaneously establish the C-3 and C-7 stereocenters (Scheme 47). When the mixture of oxindole isomers **259** was treated with stoichiometric TsOH in $CHCl_3$ at reflux, two separable diastereomers **261a** and **261b** were obtained in 73% yield in a 10:1 ratio. Apparently, the reaction proceeded via two transition states **260a** and **260b**.

The natural major isomer **261a** with the desired (7*S*)-configuration was produced from the favored transition state **260a**, in which an electronic repulsion between the oxonium cation and the hydroxy group of the enol functionality is avoided. In contrast, the disfavored transition state **260b**, in which both electron repulsion and a steric effect are present, led to the unnatural minor isomer **261b** with the inverse (7*R*)-configuration. After having successfully synthesized **261a**, which possessed all the ring systems and correct stereochemistry of the carbon stereocenters of the target (+)-gelsemine, attention turned to the final task of converting the nitrile substituent at C-20 in **261a** to an ethylene substituent. After removal of the methoxy group in **261a** by hydrogenation with 5% Pd/C, the nitrile group in **262a** was reduced to an aldehyde group to provide oxindole **264** in 71% yield in two steps. The olefination of aldehyde **263** with the Tebbe's reagent yielded (+)-gelsemine 264 in 60% yield (Scheme 47).[46]

3.6 Garg et al's total synthesis of (–)-*N*-methylwelwitindolinone C isothiocyanate, (+)-*N*-methylwelwitindolinone D isonitrile, and (–)-*N*-methylwelwitindolinone B isothiocyanate.

*3.6.1 Synthesis of (–)-*N*-methylwelwitindolinone C isothiocyanate.* Garg et al's synthesis began with the concise preparation of enone **271a** (Scheme 48).[47] The (*S*)-carvone **265** was elaborated to enone **271a** using a robust five-step procedure

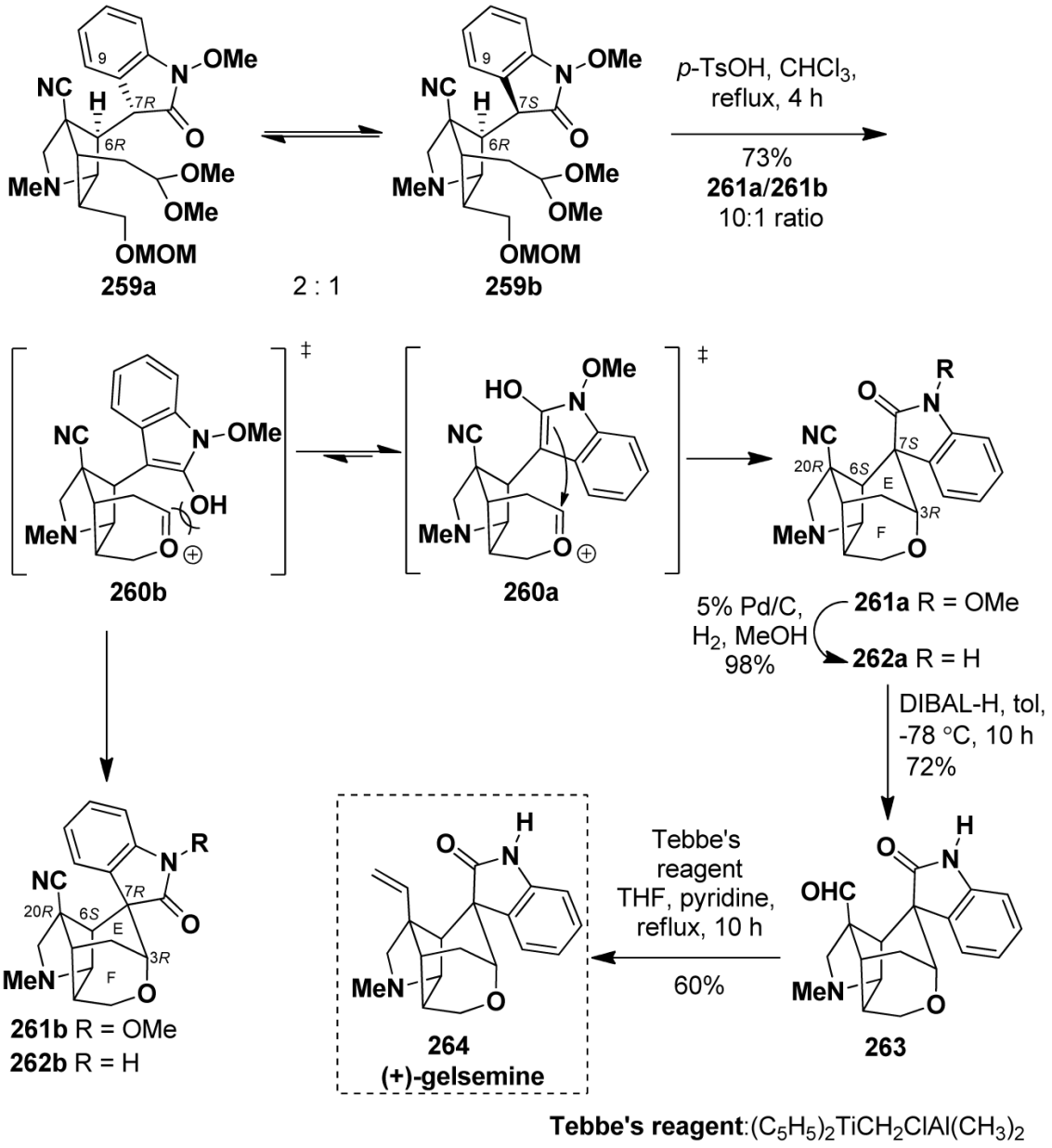


Scheme 46. Synthesis of oxindole intermediate **259**.

reported by Sakagami et al in the enantiomeric series.[48] With easy access to enone **271a**, the cleavage of the pivalate group was followed by I_2-promoted addition of 5-bromoindole **272**, to furnish indole adduct **273** in 54% yield over two steps (Scheme 49).[49] The TBS protection of **273** provided silyl ether **274**, which in turn was employed in the critical indolyne cyclization process.

Treatment of **274**, with $NaNH_2$ and *tert*-BuOH in THF at ambient temperature, led to indolyne adducts **275** and **276** in a combined 46% yield (2.5:1 ratio).[50a,b] Although *O*-arylated product **276** was observed, the major product **275** possessed the desired [4.3.1]-bicyclic framework of the natural product and was available in gram quantities (Scheme 49).

Since the bicyclic framework of the natural product was assembled, Garg et al turned their efforts toward the introduction of the vinyl chloride and oxindole moieties into **275** (Scheme 50). Desilylation of **275**, followed by Dess–Martin oxidation, smoothly furnished diketone **277**.



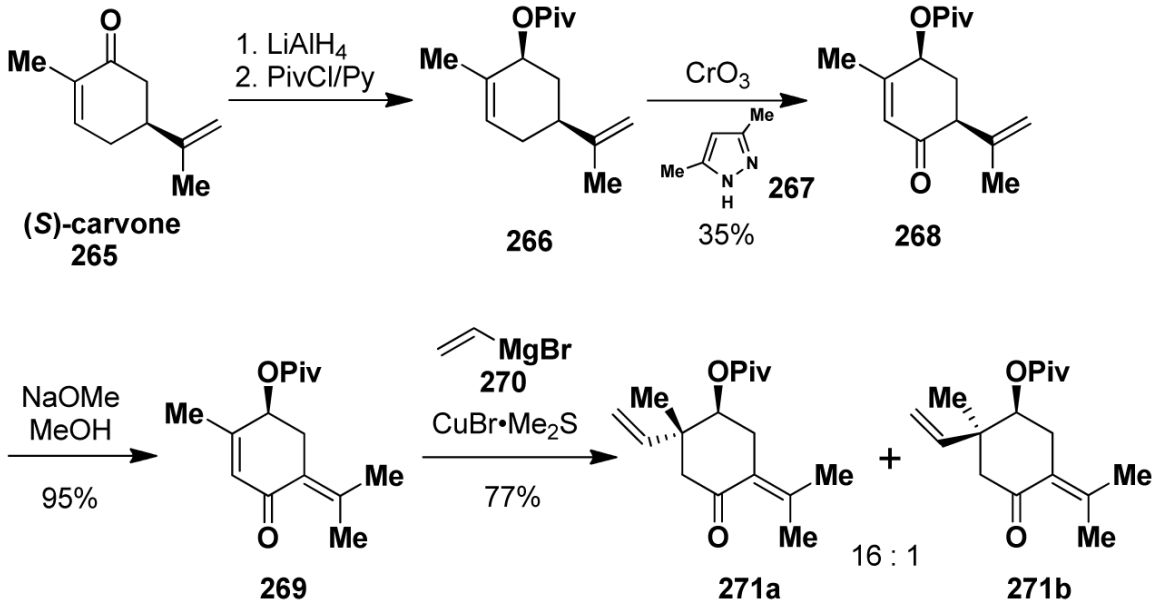
Scheme 47. Synthesis of (+)-gelsemine **264**.

Subsequently, a sequence involving triflation and Pd-catalyzed stannylation provided vinyl stannane **278**.[51] Exposure of the latter to $CuCl_2$ in dioxane afforded vinyl chloride **279**.[52] To arrive at the necessary oxindole, a two-step procedure, which involved sequential C-2 bromination and hydrolysis, was employed to deliver late-stage intermediate vinyl chloride **280** (Scheme 50).

With intermediate **280** lacking only the isothiocyanate substituent, attention turned to functionalization of the sterically congested C-11 bridgehead position (Scheme 51). It was postulated that an intramolecular nitrene C-H insertion was a way to achieve the total synthesis. Consequently, ketone reduction of **280** proceeded efficiently using *i*-Bu_2AlH to furnish a secondary alcohol intermediate as a single diastereomer.

Subsequent carbamoylation furnished tetracycle **281**, which was the key substrate for the critical C-H insertion reaction. Upon treatment of oxindole **281** with AgOTf, bathophenanthroline, and $PhI(OAc)_2$ in CH_3CN at elevated temperatures,[53a,b] the desired nitrene insertion took place to deliver oxazolidinone **282** as the major product. Some starting material **281** was also recovered and could be recycled through the synthetic route. Nonetheless, hydrolysis of **282**, followed by IBX oxidation, generated the oxindole intermediate aminoketone **283**. Final introduction of the isothiocyanate function (according to a known procedure by Richter et al) furnished (–)-*N*-methylwelwitindolinone C isothiocyanate **285**.[54a,b]

*3.6.2 Synthesis of (+)-*N*-methylwelwitindolinone D isonitrile.* An extension of the chemistry developed by Garg

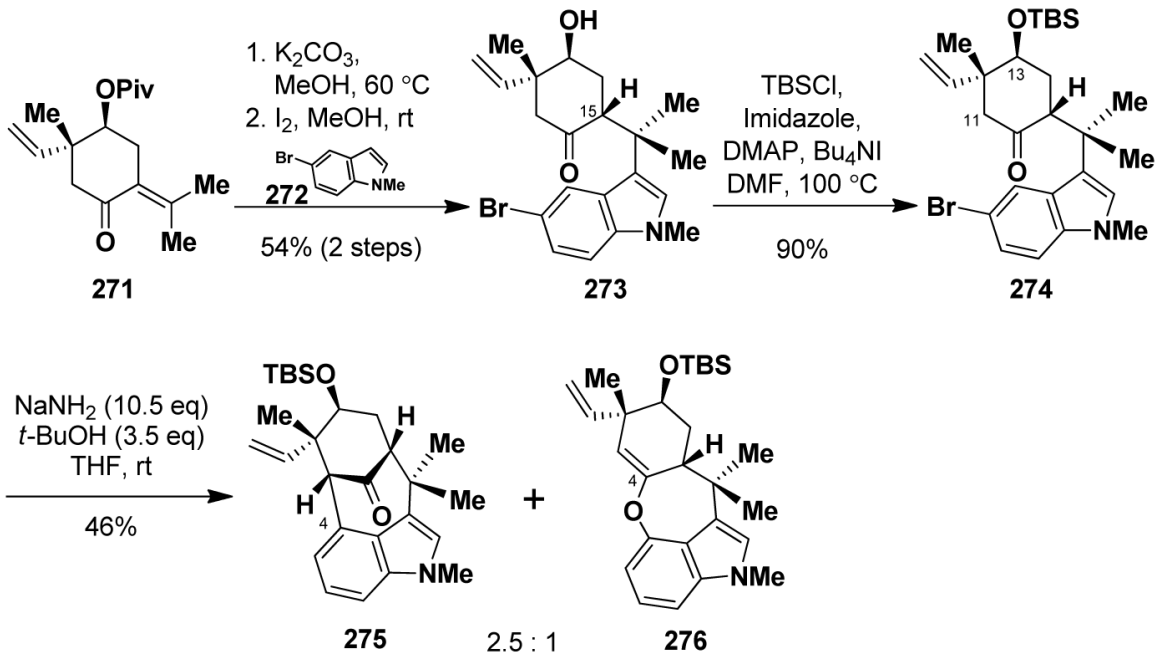


Scheme 48. Synthesis of enone **271a**.

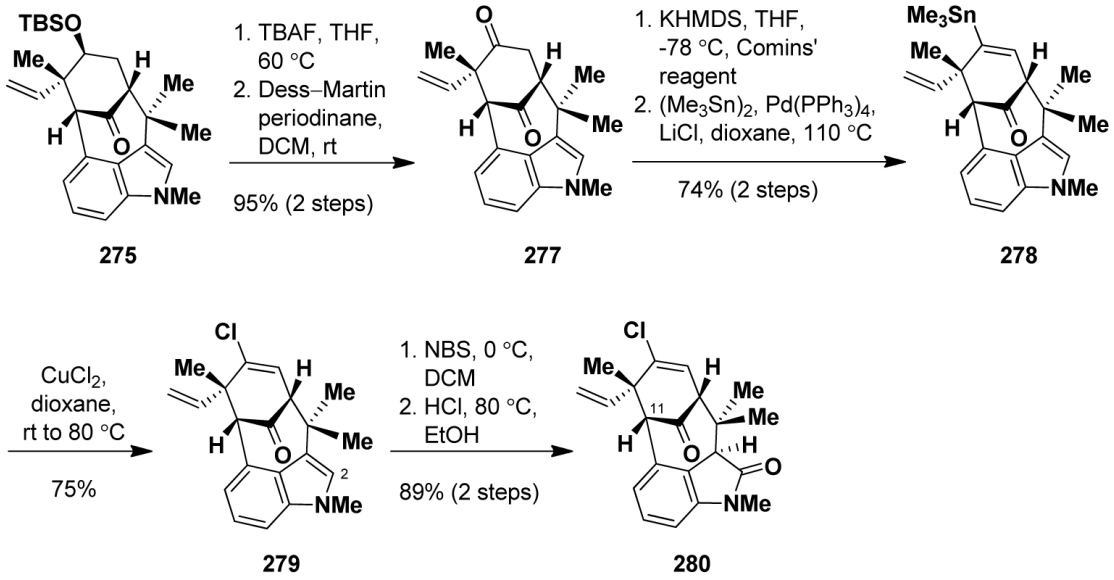
et al (see above) made possible the synthesis of (+)-*N*-methylwelwitindolinone D isonitrile **296**.[48,55] The important intermediate indole **275** (Scheme 49) was at this point converted to oxindole **286** using a one-pot oxidation/hydrolysis sequence (Scheme 52). Since the acidic conditions led to desilylation, reprotection of the alcohol was necessary to provide TBS-protected indole **287**. Deuteride reduction and carbamoylation proceeded without event to furnish deuterated-carbamate **288** in quantitative yield.

Exposure of the latter to the conditions of an Ag-promoted nitrene insertion process, seen above, furnished oxindole **289** in 70% yield. The strategic use of deuterium minimized an undesirable competitive reaction, thus giving synthetically useful yields of the desired insertion product **289**.[56] From oxindole **289**, a standard deprotection/oxidation sequence delivered key intermediate **290** (Scheme 52).

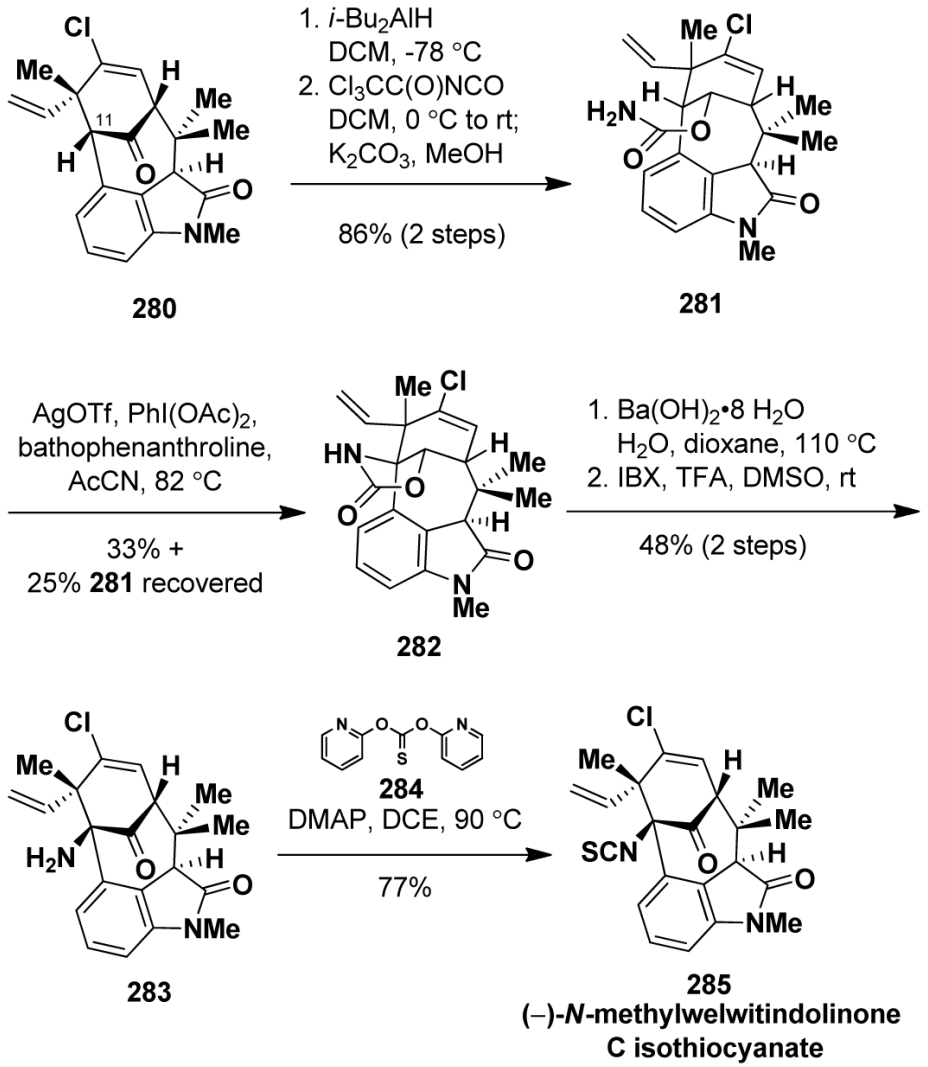
Next, Quasdorf et al found that simple exposure of **290** to TBAF in acetonitrile in the presence of air efficiently



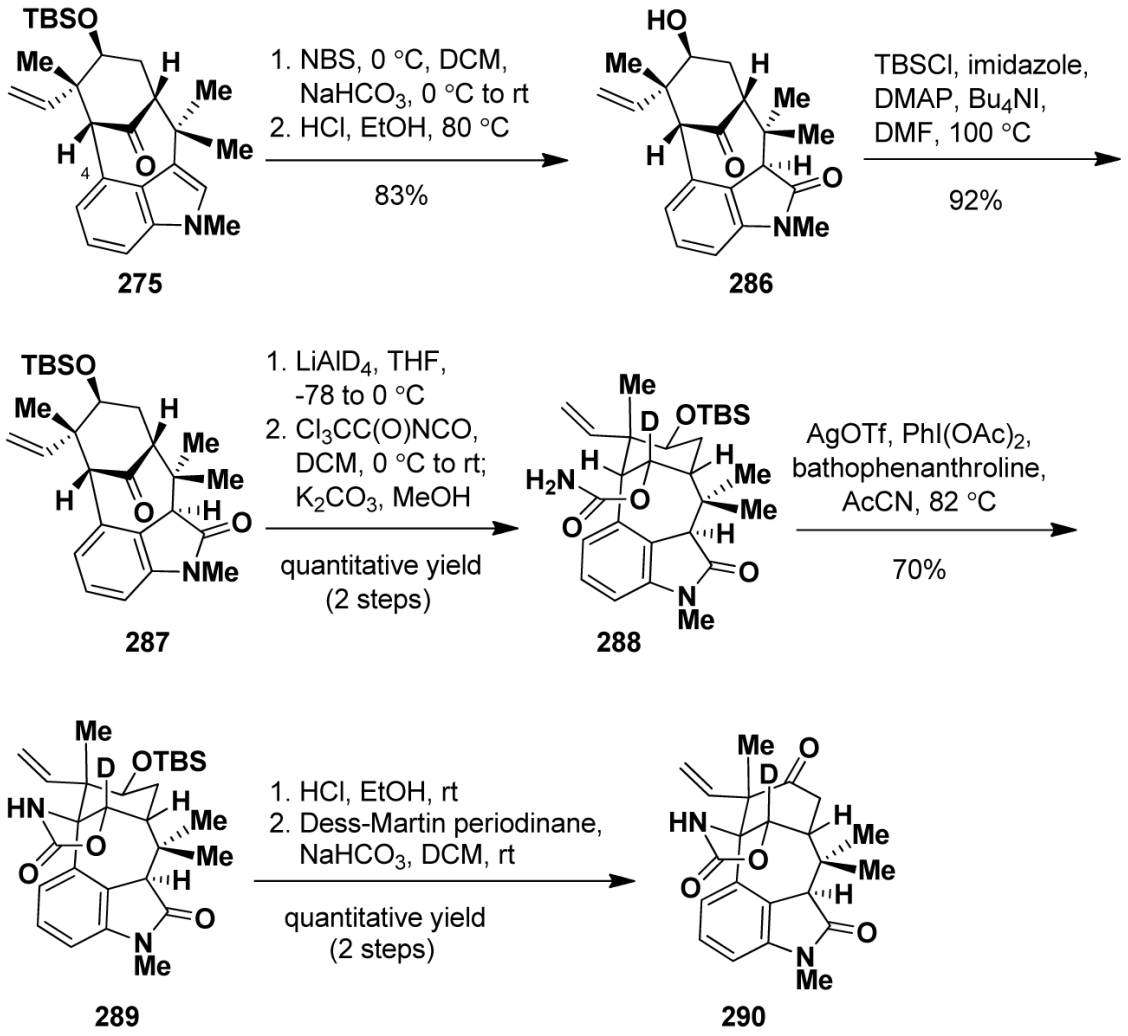
Scheme 49. Synthesis of tetracyclic indole **275**.



Scheme 50. Synthesis of tetracyclic oxindole **280**.



Scheme 51. Synthesis of (–)-*N*-methylwelwitindolinone C isothiocyanate **285**.



Scheme 52. Synthesis of key oxindole intermediate **290**.

delivered tetrahydrofuran **292** (Scheme 53).[56,57] In previous studies, it was found that TBAF/air can facilitate C-3 oxidation of oxindoles containing the welwitindolinone scaffold, but the use of TBAF/air to build an ethereal linkage through double C-H functionalization was unknown.[58a,b]

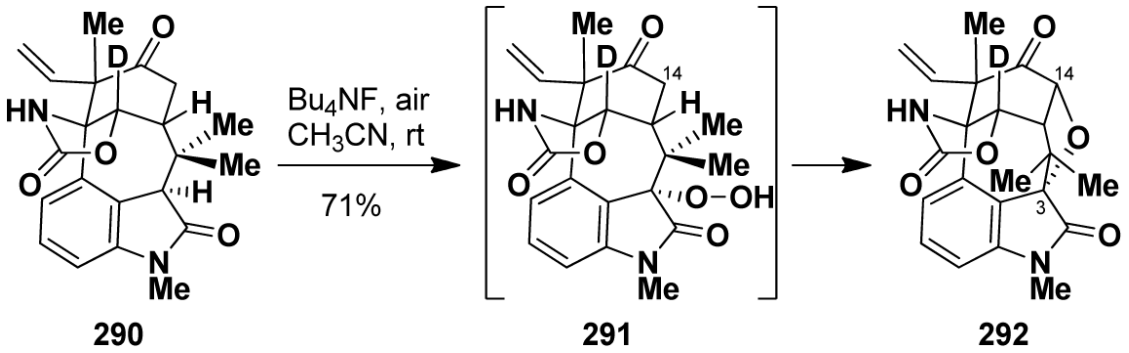
Notably, the use of other bases in place of TBAF, such as K_2CO_3 and Cs_2CO_3, also promoted the formation of **292**, albeit in lower yields. It is likely that this method for introducing the THF ring proceeded by initial diastereoselective C-3 oxidation, followed by cyclization. Related (C-3)-peroxy compounds were observed in previous studies by the Garg and Wood research groups.[55]

In order to complete the total synthesis, it remained to elaborate the cyclic carbamate to the ketone and isonitrile functional groups present in the target molecule **296** (Scheme 54). To this end, ketone **292** was reduced to the corresponding alcohol **293** with $LiAlH_4$. Upon exposure of alcohol **293** to the conditions of hydrolysis, cyclohexyl ring fragmentation was not observed, and hydrolysis gave the desired diol intermediate, which was oxidized with IBX to provide diketone **294**. Finally, formylation of the latter amine provided *N*-formyl oxindole **295**, which was directly exposed to standard dehydration conditions to deliver (+)-*N*-methylwelwitindolinone D isonitrile **296** (Scheme 54).

*3.6.3 Synthesis of (–)-*N*-methylwelwitindolinone B isothiocyanate.* Garg et al also took advantage of tetracyclic ketone **275** for the synthesis of (–)-*N*-methylwelwitindolinone B isothiocyanate **306**.[59] To this end, ketone **275** was elaborated to mesylate **297** in two steps, which involved reduction with $LiAlH_4$, followed by sulfonylation.

Upon treatment of the mesyl indole **297** with Bu_4NF in THF at 80°C, desilylation readily occurred with concomitant cyclization to afford oxabicycle **298** in 84% yield. Subsequently, a one-pot oxidation/hydrolysis protocol was used to elaborate **298** to the corresponding oxindole **299**, which was formed as a single diastereomer (Scheme 55).

With rapid access to oxabicycle **299**, Garg et al were poised to attempt the key chlorinative ring-opening reaction (Scheme 56). Alkene **299** was exposed to modified oxidative cleavage conditions, which furnished aldehyde **300**.[60]

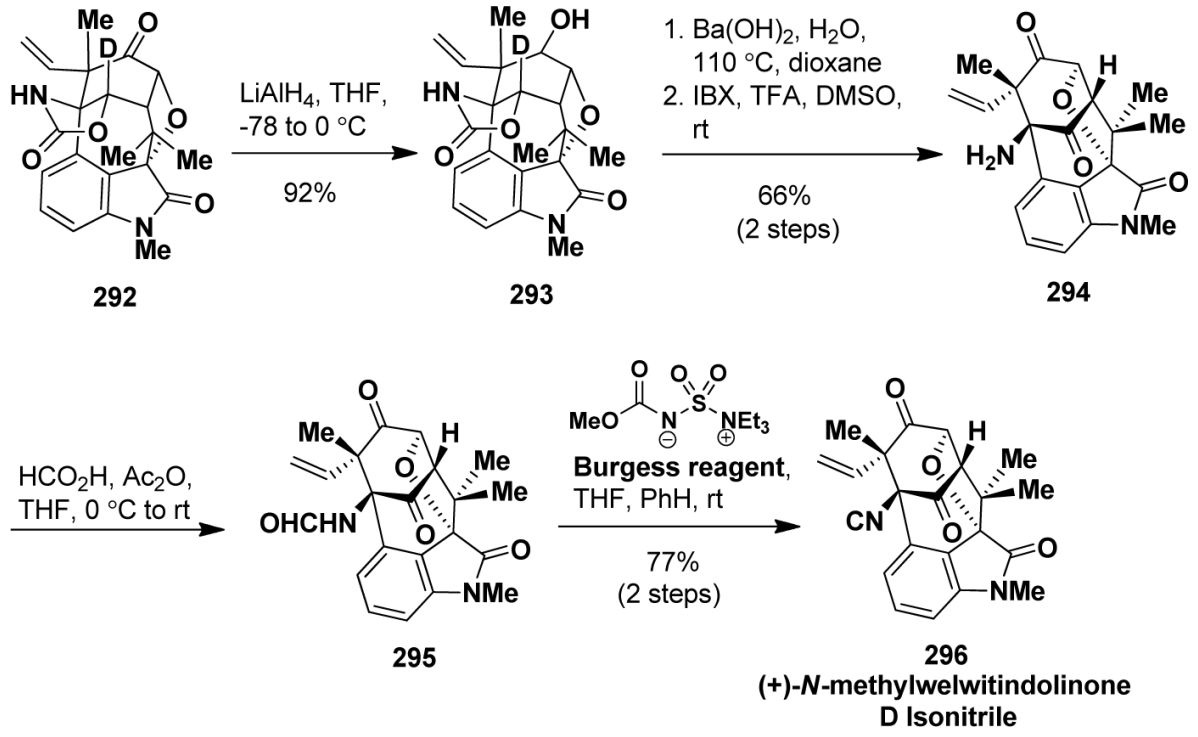


Scheme 53. Synthesis of intermediate **292**.

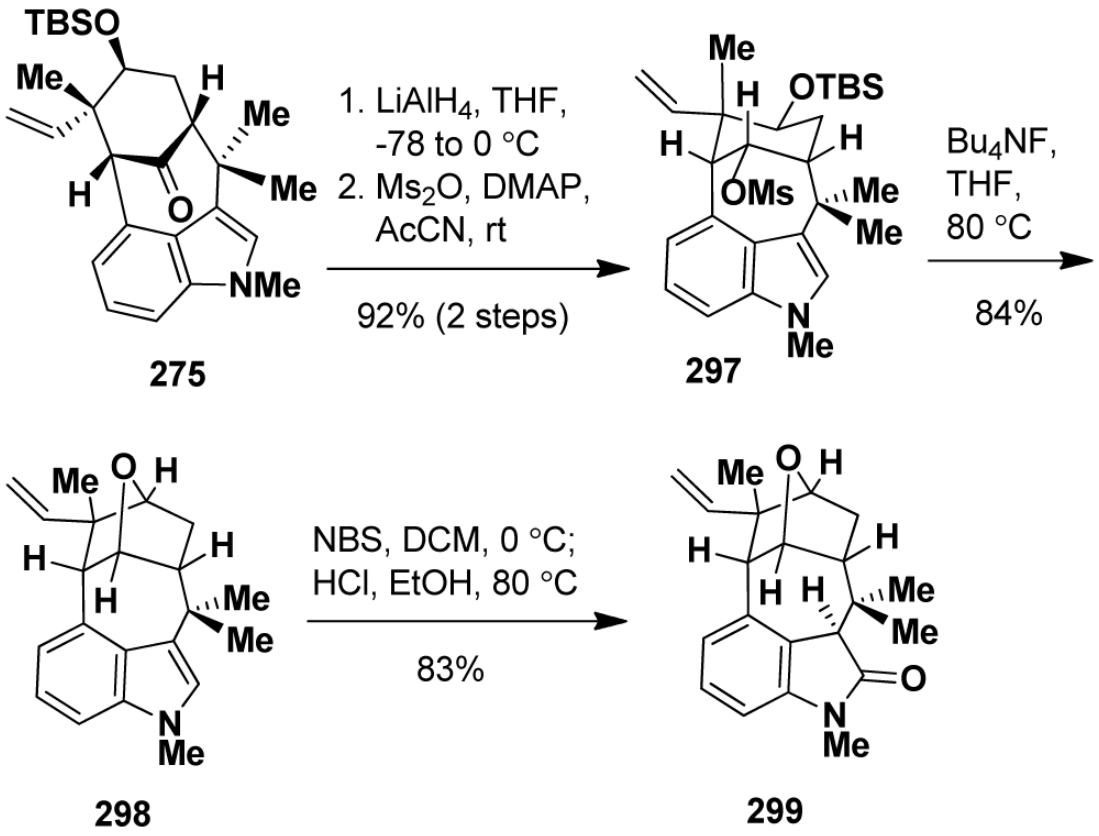
Treatment of **300** with BCl_3 in CH_2Cl_2 at 50°C delivered the desired chlorinated product **301** in 64% yield as a single diastereomer.

In order to finish the synthesis of the target molecule, oxidation of alcohol **301** (Scheme 57), followed by Wittig olefination, afforded ketone **302**. Subsequent reduction of **302** with $LiAlD_4$ occurred with complete diastereoselectivity to furnish an alcohol intermediate, which was carbamoylated to provide carbamate **303**. Carbamate **303** proved to be a viable substrate for the desired nitrene insertion reaction; upon treatment of **303** with AgOTf, $PhI(OAc)_2$, and bathophenanthroline in CH_3CN at 50°C, the C-11 functionalized product **304** was obtained in 55% yield (with 10% recovered starting material). With the latter insertion product **304** in hand, all that remained to complete the total synthesis of the target molecule was cleavage of the carbamate, followed by oxidation and N-functionalization.

Despite previous success involving carbamate hydrolysis on related compounds, Garg et al found that treatment of **304** with $Ba(OH)_2$ led to decomposition of the alkyl chloride. This led them to develop a milder means for cleavage of the carbamate. Prompted by the report of Morin et al, cleavage of *N,N*-dialkylcarbamate derivatives of phenols,[61] cyclic carbamate **304** (Scheme 57), was exposed to the Schwartz's reagent $[(C_5H_5)_2Zr(H)Cl]$ in THF. In this way, the carbamate was cleaved selectively to give an amidoalcohol intermediate, where C-23 of **304** had conveniently been retained as a formyl group on the bridgehead nitrogen. Oxidation of the alcohol



Scheme 54. Synthesis of (+)-*N*-methylwelwitindolinone D isonitrile **296**.



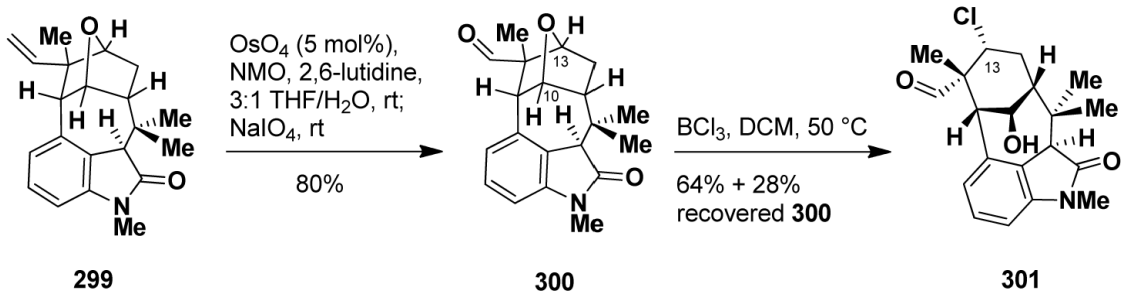
Scheme 55. Synthesis of oxabicycle **299**.

intermediate delivered formyl amide **305**. With the chloride still intact, dehydration with Burgess's reagent (Scheme 57) and sulfurization afforded (–)-*N*-methylwelwitindolinone B isothiocyanate **306**.[62]

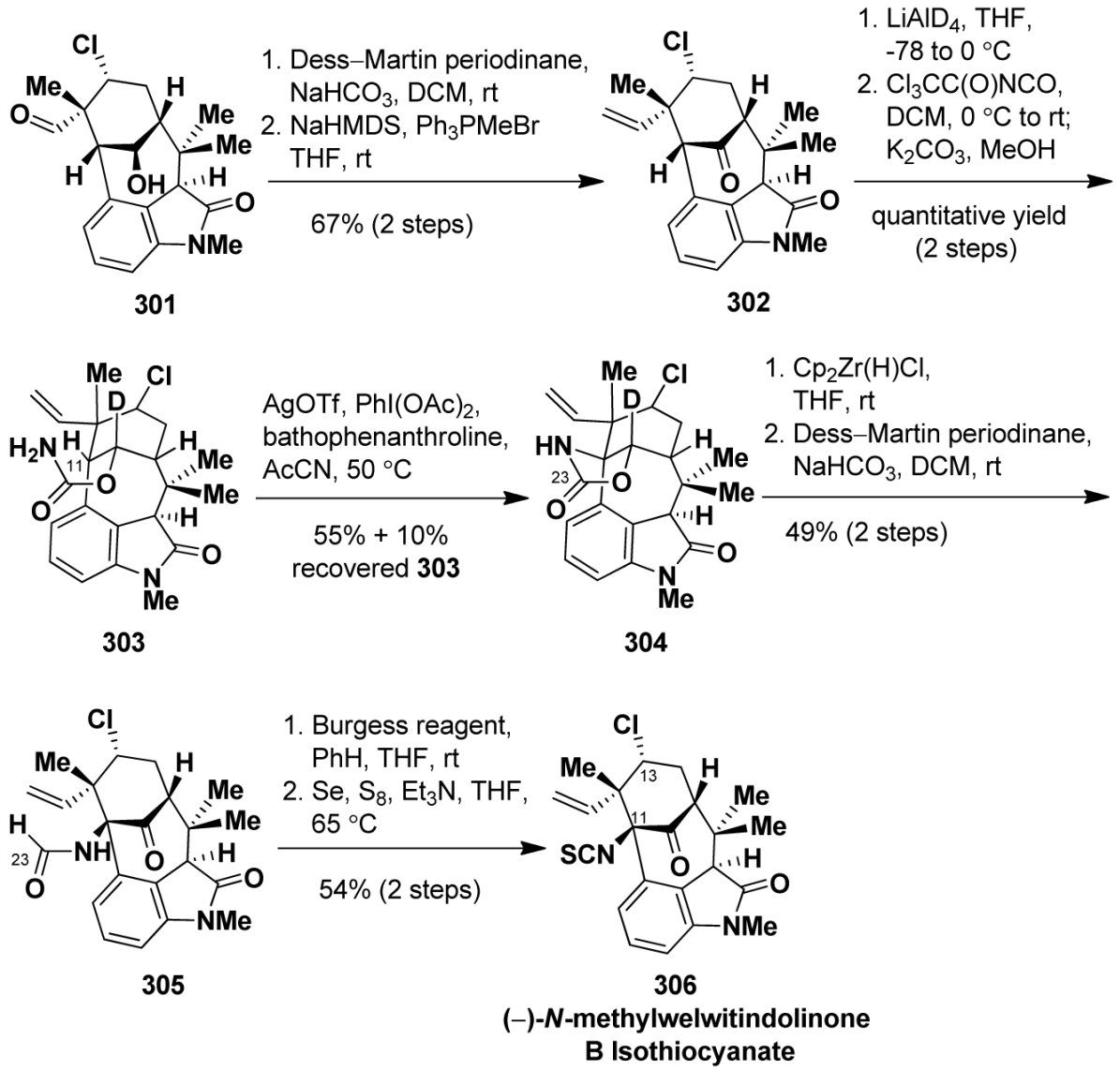
3.7 Rawal et al's synthesis of *N*-methylwelwitindolinone D isonitrile, (–)-*N*-methylwelwitindolinone C isothiocyanate, (–)-*N*-methylwelwitindolinone C isonitrile, and (–)-3-hydroxy-*N*-methylwelwitindolinone C isothiocyanate.

3.7.1 Synthesis of N*-methylwelwitindolinone D isonitrile.* Rawal et al reported a concise total synthesis of (±)-*N*-methylwelwitindolinone D isonitrile **296**,[63] the first in a family of complex bicyclo[4.3.1]decane containing indole alkaloids to yield to synthesis. The complete carbon core of the natural product was assembled rapidly through a Lewis acid-mediated alkylative coupling process, and this was followed directly by a palladium-catalyzed enolate arylation reaction. The final ring of the pentacycle was introduced by an indole oxidation/cyclization, and the isonitrile was installed through the rearrangement of an aldehyde to an isothiocyanate, followed by desulfurization.

In preparation for the alkylative coupling, Rawal et al sought to quickly assemble the two partners, **318** and **319**, from readily available materials (Scheme 59).[63] Vinylogous ester **315** was prepared by addition of vinyl cuprate to



Scheme 56. Synthesis of oxindole **301**.



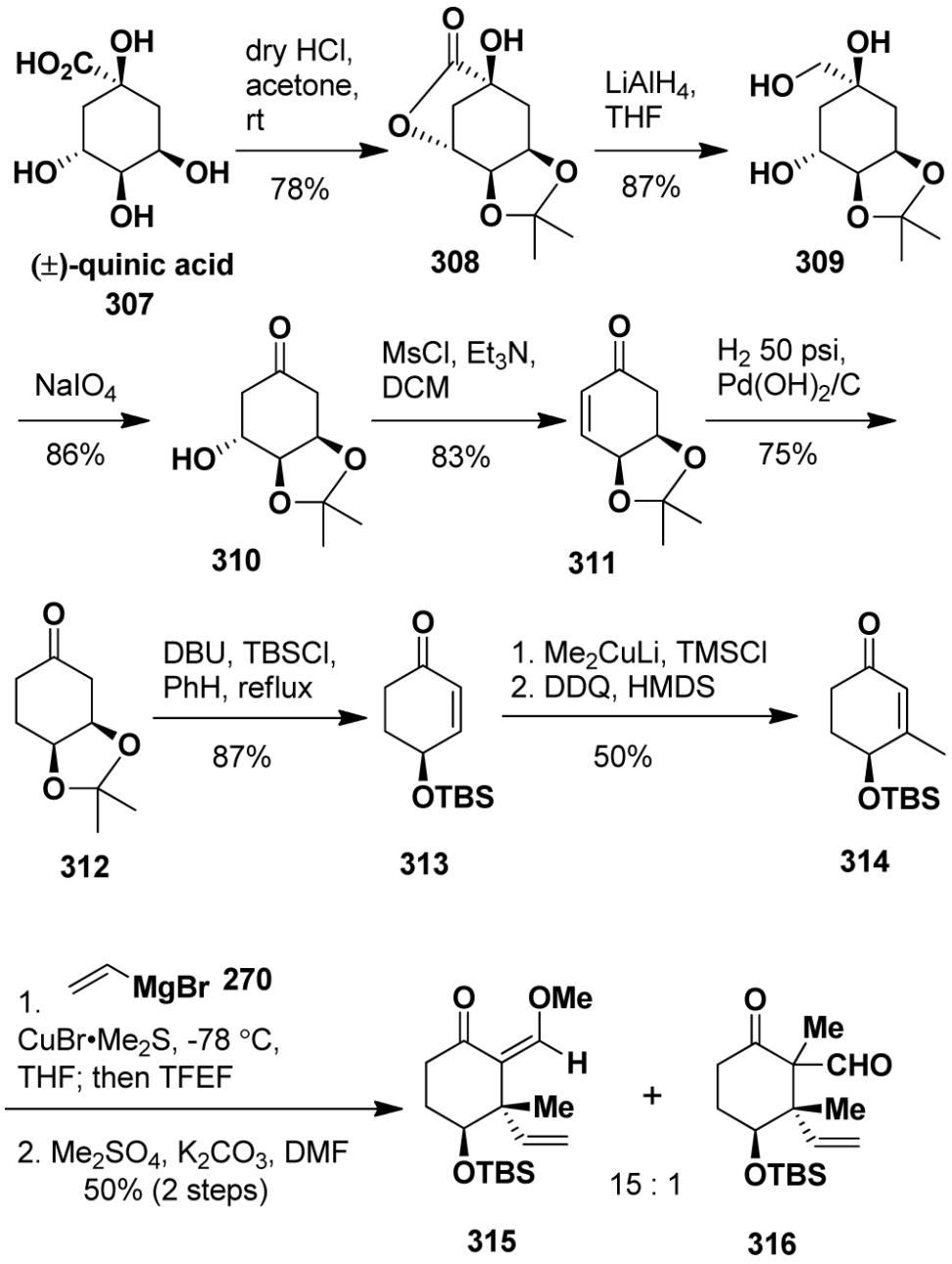
Scheme 57. Synthesis of (–)-*N*-methylwelwitindolinone B isothiocyanate **306**.

the known enone **314**, which was prepared as described in the literature from quinic acid **307** (Scheme 58),[64] followed by quenching the intermediate enolate with Zayia's reagent, 2,2,2-trifluoroethyl formate (TFEF).[65] Methylation of the resultant vinylogous acid then provided ester **315** in 47% overall yield, together with trace quantities of the C-methylation product, ketoaldehyde **316**. Indole coupling partner **318** was prepared from 3-acetyl-4-bromo indole **317** upon addition of methylmagnesium bromide to it (Scheme 59).

With the two required fragments in hand, they set forth on the crucial alkylative coupling. Vinylogous ester **315** was converted to silyl enol ether **319** (Scheme 59). The reaction of silyl enol ether **319** and *N*-methyl indole alcohol **318** promoted with TMSOTf offered the best results.

The rationale behind this approach was that an electron-rich *N*-methyl indole and the weakly basic triflate counterion would better stabilize the transient benzylic cation. Aqueous acidic workup of the reaction mixture afforded vinylogous acid **320** as a single diastereomer in 78% overall yield (Scheme 59).

Completion of the bicyclo[4.3.1]decane framework was expected to be accomplished using a palladium-catalyzed intramolecular enolate arylation to form the key C-4/C-11 bond (Scheme 60). This transformation presented a notable challenge in that it would set in place vicinal quaternary stereocenters. Moreover, the transition metal-catalyzed α-arylation of a β-ketoaldehyde was without precedent. An evaluation of palladium sources, ligands, bases, and solvents ultimately identified $Pd(OAc)_2$ and tri-*tert*-butylphosphine (1:1) as the optimum catalyst system. The use of this catalyst complex in combination with KHMDS in toluene afforded the desired tetracycle **321** in 73% yield. Next, attention turned to the installation of the spirocyclic tetrahydrofuran, the final ring in the pentacyclic structure of the natural product.

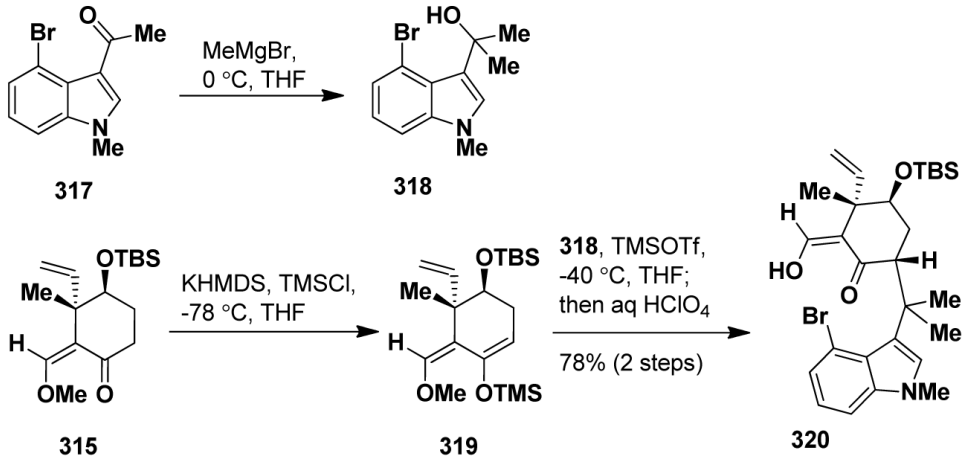


Scheme 58. Preparation of enone **315**.

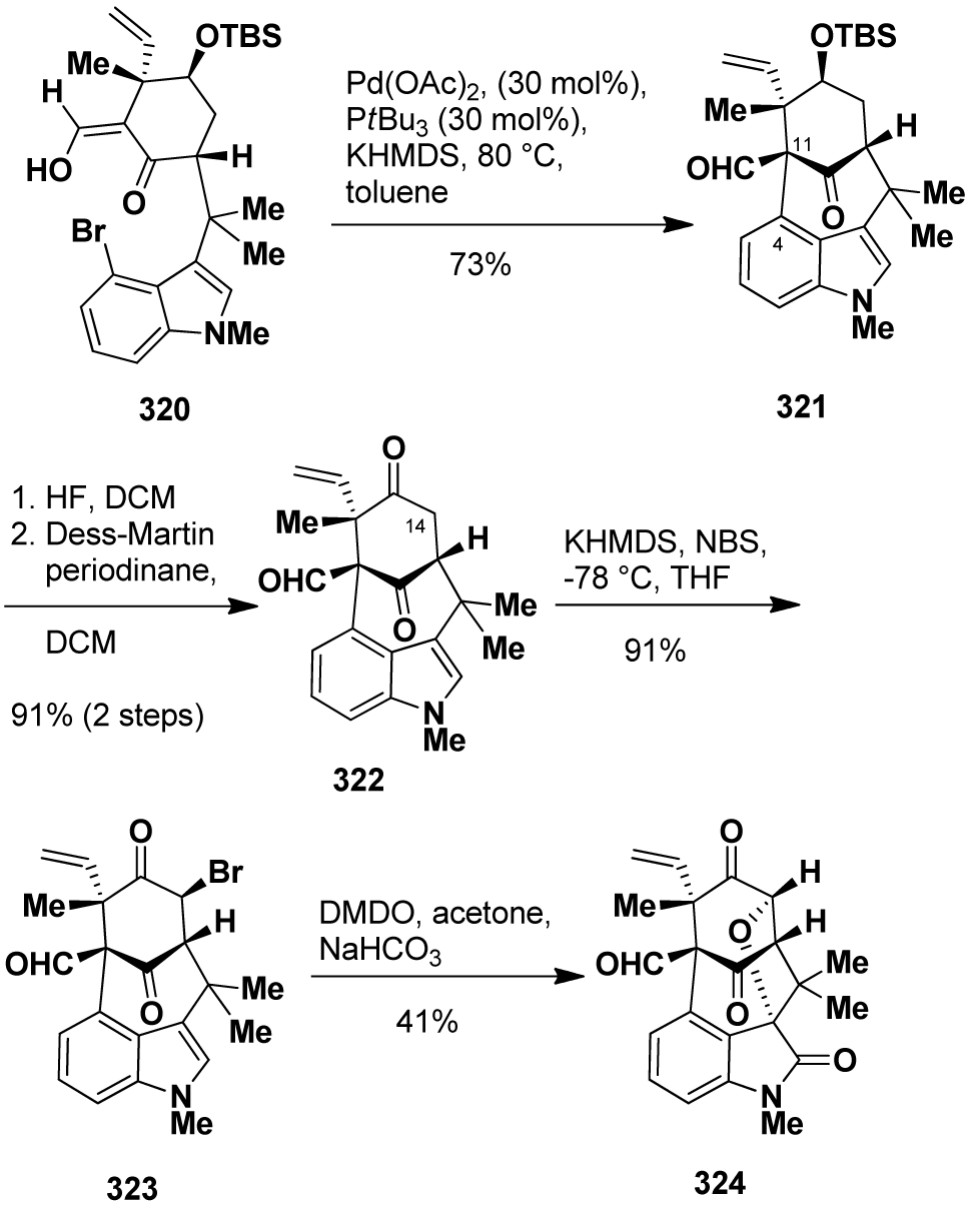
To this end, the TBS group in **321** was removed with HF, and the alcohol, which resulted, was oxidized using the Dess–Martin reagent to give diketone **322** (Scheme 60). In view of the caged architecture of this tetracycle, α-bromination to the ketone at C-14 was expected to occur selectively from the convex face. In any event, deprotonation of **322** with KHMDS and treatment of the resulting enolate with *N*-bromosuccinimide gave rise to bromodione **323** as a single diastereomer, with the halide ideally oriented for subsequent intramolecular displacement from the opposite face.

Critical for the displacement reaction was selective introduction of the hydroxyl group at C-3 through oxidation of the indole moiety. Importantly, when **323** was subjected to reaction with a freshly prepared solution of DMDO, this process not only resulted in the desired diastereoselective oxidation of the indole to the 3-hydroxyoxindole but also a spontaneous cyclization of this intermediate to furnish the desired pentacycle **324** (Scheme 60).

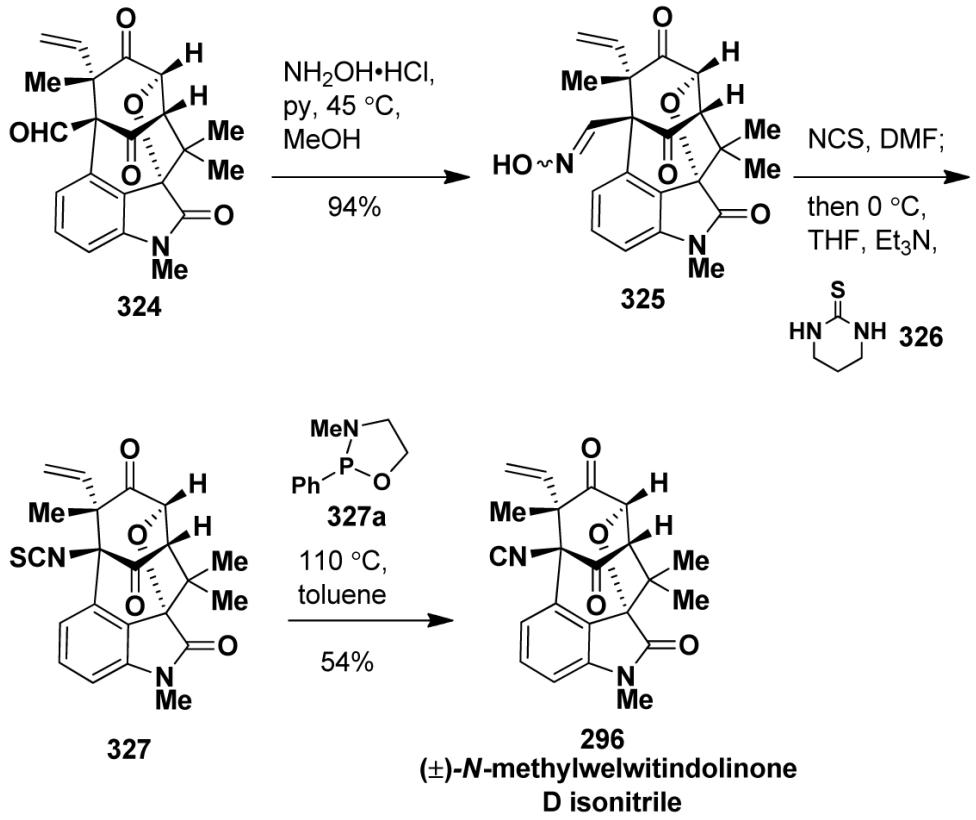
In order to finish the synthesis, aldehyde **324** was converted to the corresponding oxime **325** (Scheme 61). By following Kim et al's one-pot protocol,[66a,b] oxime oxime **325** was treated with *N*-chlorosuccinimide, followed by propylenethiourea **326** and triethylamine, to give isothiocyanate **327** in 65% yield. This transformation was postulated to proceed through a nitrile oxide, which then reacted with the thiourea to give an oxathiazoline through a formal [3 + 2] cycloaddition



Scheme 59. Synthesis of bromo indole **320**.



Scheme 60. Synthesis of oxindole intermediate **324**.



Scheme 61. Synthesis of *N*-methylwelwitindolinone D isonitrile **296**.

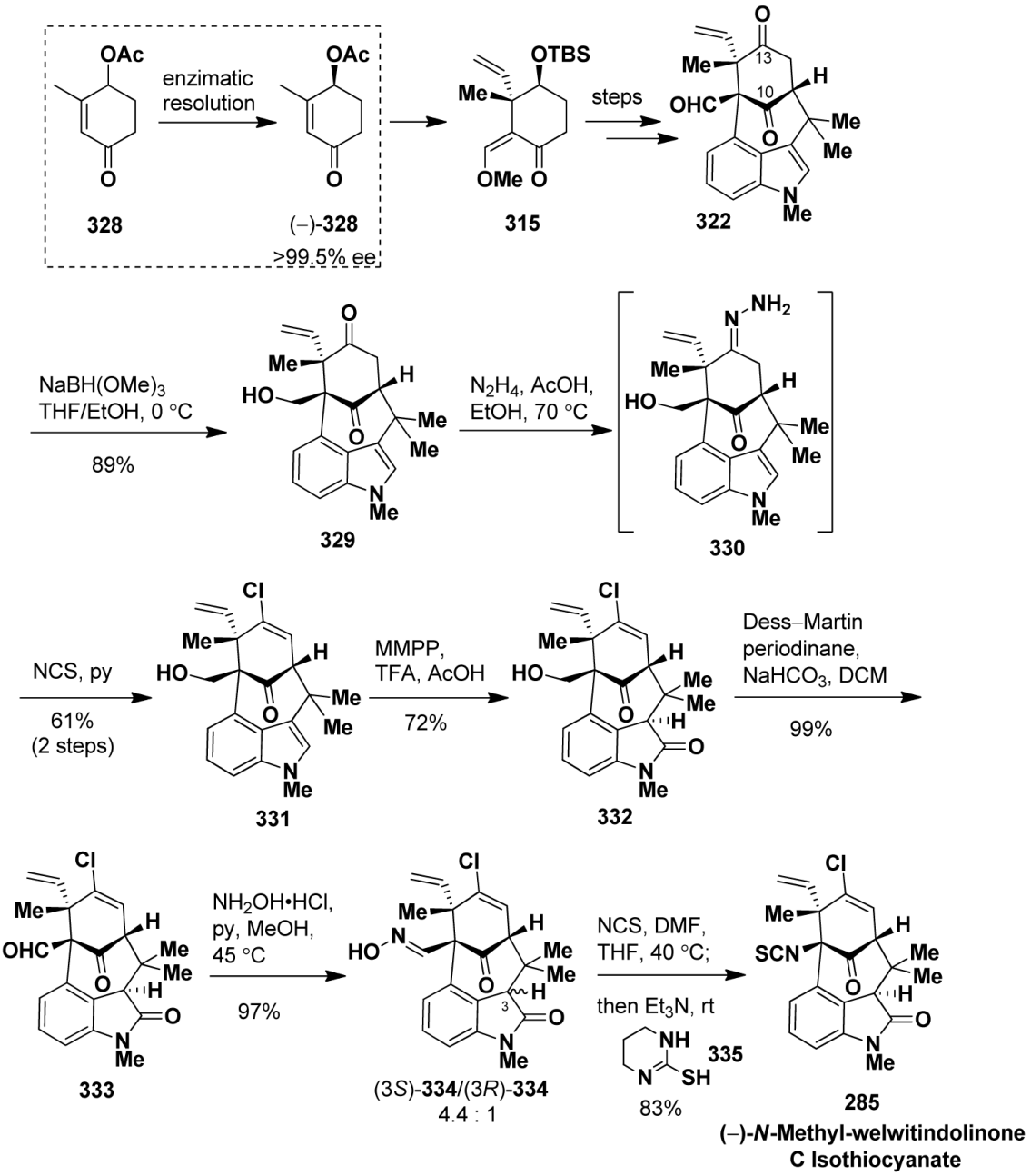
reaction. Rearrangement of the putative oxathiazoline then afforded the isothiocyanate. Finally, desulfurization of the isothiocyanate was realized using oxazaphospholidine **327** to provide *N*-methylwelwitindolinone D isonitrile **296** in 54% yield (Scheme 61).[67]

*3.7.2 Synthesis of (–)-*N*-methylwelwitindolinone C isothiocyanate, (–)-*N*-methylwelwitindolinone C isonitrile, and (–)-3-hydroxy-*N*-methylwelwitindolinone C isothiocyanate.* As part of a comprehensive strategy to the welwitindolinone alkaloids possessing a bicyclo[4.3.1]-decane core,[68] Rawal et al reported the concise asymmetric total synthesis of (–)-*N*-methylwelwitindolinone C isothiocyanate **285**, (–)-*N*-methylwelwitindolinone C isonitrile **336**, and (–)-3-hydroxy-*N*-methylwelwitindolinone C isothiocyanate **337** from a common tetracyclic intermediate **322**. Their approach toward *N*-methylwelwitindolinone C isothiocyanate **285** was based on late-stage introduction of the vinylic chloride functional group through electrophilic chlorination of hydrazone **329** (Scheme 62), which would be available from ketone **322**. It was envisioned that the use of this compound **322**, whose racemic synthesis was established en route to *N*-methylwelwitindolinone D isonitrile (**296**, as discussed before), would provide a strategic branching point from which to target several members of this alkaloid family.

In order to realize an asymmetric synthesis of (–)-**285**, key intermediate **322** was prepared from enantioenriched acetate (–)-**328** (>99.5% ee), which was obtained through pig liver esterase-catalyzed resolution of racemic 4-acetoxy-3-methylcyclohexenone (Scheme 62).[69]

A key challenge in the route was the installation of the vinyl chloride moiety at C-13. Rawal et al's plan was to introduce the chloride through electrophilic chlorination of the C-13 hydrazone.[70a,b] Of the three different carbonyl groups in the starting tetracycle **322**, the least likely to condense with hydrazine was the bridging ketone at C-10, due to its congested steric environment. In order to avoid formation of the hydrazone with the remaining aldehyde carbonyl, the idea was to protect this functionality as the corresponding alcohol **329**. Thus, treatment of tricarbonyl **322** with $NaBH(OMe)_3$ chemoselectively reduced the aldehyde (Scheme 62), which was then condensed with hydrazine at high temperatures in the presence of acetic acid to give the desired hydrazone **330** selectively.

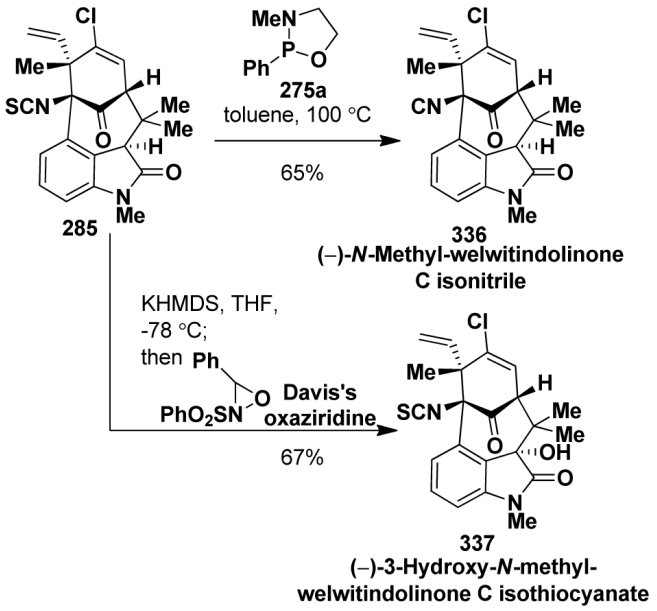
Subsequent exposure of the crude hydrazone **330** to *N*-chlorosuccinimide in pyridine afforded vinyl chloride **331** in 61% yield. The next task was the oxidation of the indole, which proceeded cleanly when mild-oxidant, magnesium monoperoxyphthalate (MMPP) was used, to afford oxindole **332** in 72% yield. Since the primary alcohol had served its purpose, it was returned to the aldehyde state (compound **333**) in nearly quantitative yield using Dess–Martin periodinane. The condensation of aldehyde **333** with hydroxylamine provided a variable mixture of separable oximes



Scheme 62. Synthesis of (–)-*N*-methyl-welwitindolinone C isothiocyanate **285**.

[(3*S*)-**334** and (3*R*)-**334**, 1.6:1 to 4.4:1], epimeric at C-3. The formation of the (3*S*)-diastereomer was noteworthy, as this stereochemistry was found in at least one member of the welwitindolinone family.[71] Interestingly, the mixture of oxime diastereomers ultimately proved inconsequential, since both diastereomers, when subjected to the modified protocol for the Kim et al's oxime rearrangement,[66a,b] were converted smoothly to (–)-*N*-methylwelwitindolinone C isothiocyanate **285**.

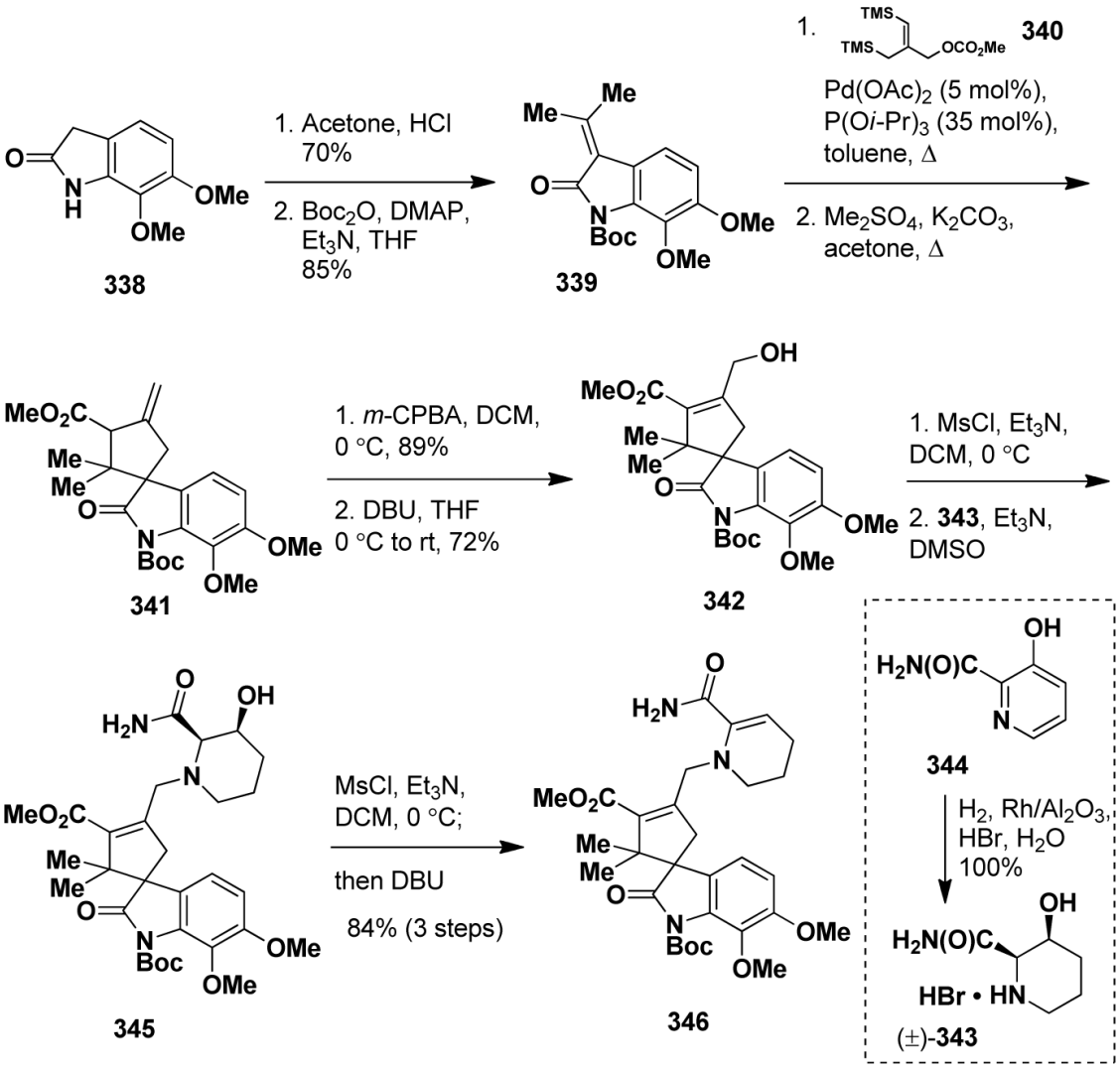
With an efficient route to *N*-methylwelwitindolinone C isothiocyanate **285** at hand, the next goal was to find pathways by which this product could be directly converted to its related alkaloids, *N*-methylwelwitindolinone C isonitrile **336**, and 3-hydroxy-*N*-methylwelwitindolinone C isothiocyanate **337** (Scheme 63). Desulfurization of isothiocyanate **285** with Mukaiyama's oxazaphospholidine **275a** gave rise to the first of these targets,[67] isonitrile **336**, in 65% yield. Conversion of **285** to hydroxyoxindole **337** posed a greater challenge, given the susceptibility of sulfur to oxidants and the need for diastereoselective oxidation. Based on prior work, the conformation of the natural product was expected to provide some measure of diastereocontrol during oxidation. Indeed, it was found that treatment of **285** with KHMDS, followed by the Davis oxaziridine reagent, afforded a single compound **337** in 67% yield.



Scheme 63. Synthesis of final natural oxindole **336** and **337**.

3.8 Trost et al's synthesis of marcfortine B and (–)-marcfortine C. The marcfortines are complex secondary metabolites that show potent antihelmintic activity and are characterized by the presence of a bicyclo[2.2.2]diazaoctane fused to a spirooxindole. Trost et al recently reported the synthesis of two members of this family.

3.8.1 Synthesis of (±)-marcfortine B. The synthesis of (±)-marcfortine B **358** began with the preparation of isopropylidene oxindole **339** from the known oxindole **338** in two steps (Scheme 64), and it subsequently underwent a highly efficient cycloaddition with silyl donor **340** in the presence of 5 mol% palladium(II) acetate and 35 mol% triisopropyl phosphite.[72,73] After hydrolytic workup and alkylation, methyl ester **341** was isolated in excellent yield as a 1:1 mixture of diastereomers. The use of dimethyl sulfate/potassium carbonate was chosen over the alternative conditions for methylation (eg, DCC/methanol or DBU/CH_3I), and this minimized any isomerization of the double bond. Moreover, this process provided higher yields than in the case of the optimized



Scheme 64. Synthesis of spirooxindole **346**.

conditions, utilizing either CH_2N_2 or $TMSCHN_2$. The mixture of diastereomeric oxindoles **341** was used as is, since the allylic stereocenter was subsequently destroyed and, therefore, of no consequence. The *exo*-methylene group was converted by an epoxidation–elimination to allylic alcohol **342**, and the pipecolic acid derivative was introduced by way of mesylation and S_N2 coupling with amine **343**, to provide an unstable secondary alcohol **345**, which was immediately subjected to the conditions for elimination to generate olefin **346** in good overall yield (Scheme 64).

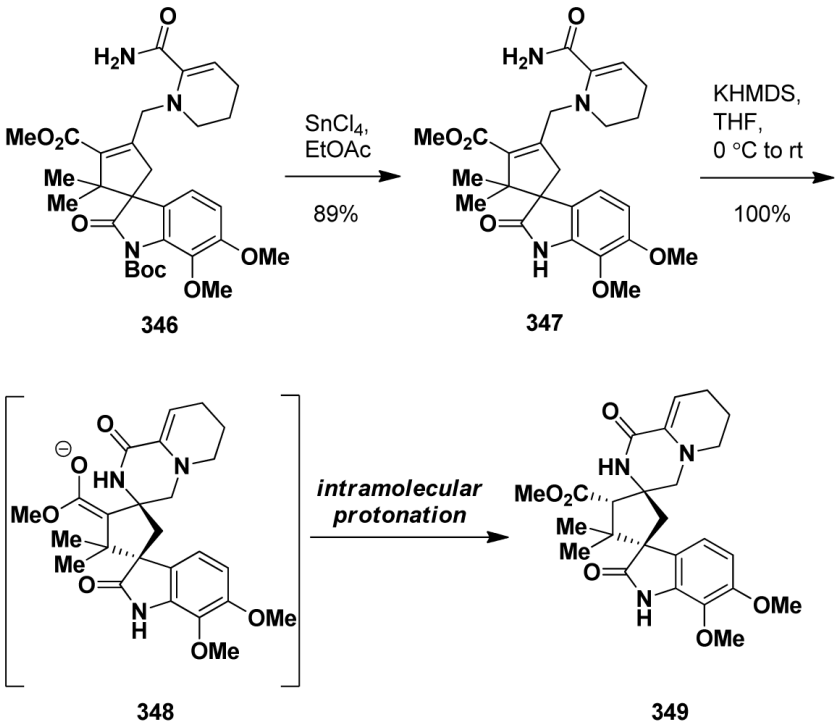
The removal of the *tert*-butyl carbamate (Boc) protecting group for the Michael cyclization proved to be necessary to avoid decomposition. The deprotection was achieved with tin tetrachloride in ethyl acetate (Scheme 65).[74] Intramolecular Michael addition was induced by treatment of the amide **347** with either 2–3 equivalents of sodium hydride or potassium hexamethyldisilazide in THF. The unsubstituted amide **347** gave exclusively the desired diastereomer **349** in excellent yield. This can be rationalized by an internal protonation of the ester enolate **348** in the case of the derivative with a free amide proton **347** (Scheme 65).

Due to the poor solubility of pentacycle **349**, reprotection of the free amide nitrogen of the oxindole was necessary, wherein the best results were obtained using *p*-methoxybenzyl (PMB) chloride in acetone with potassium carbonate as the base (Scheme 66).

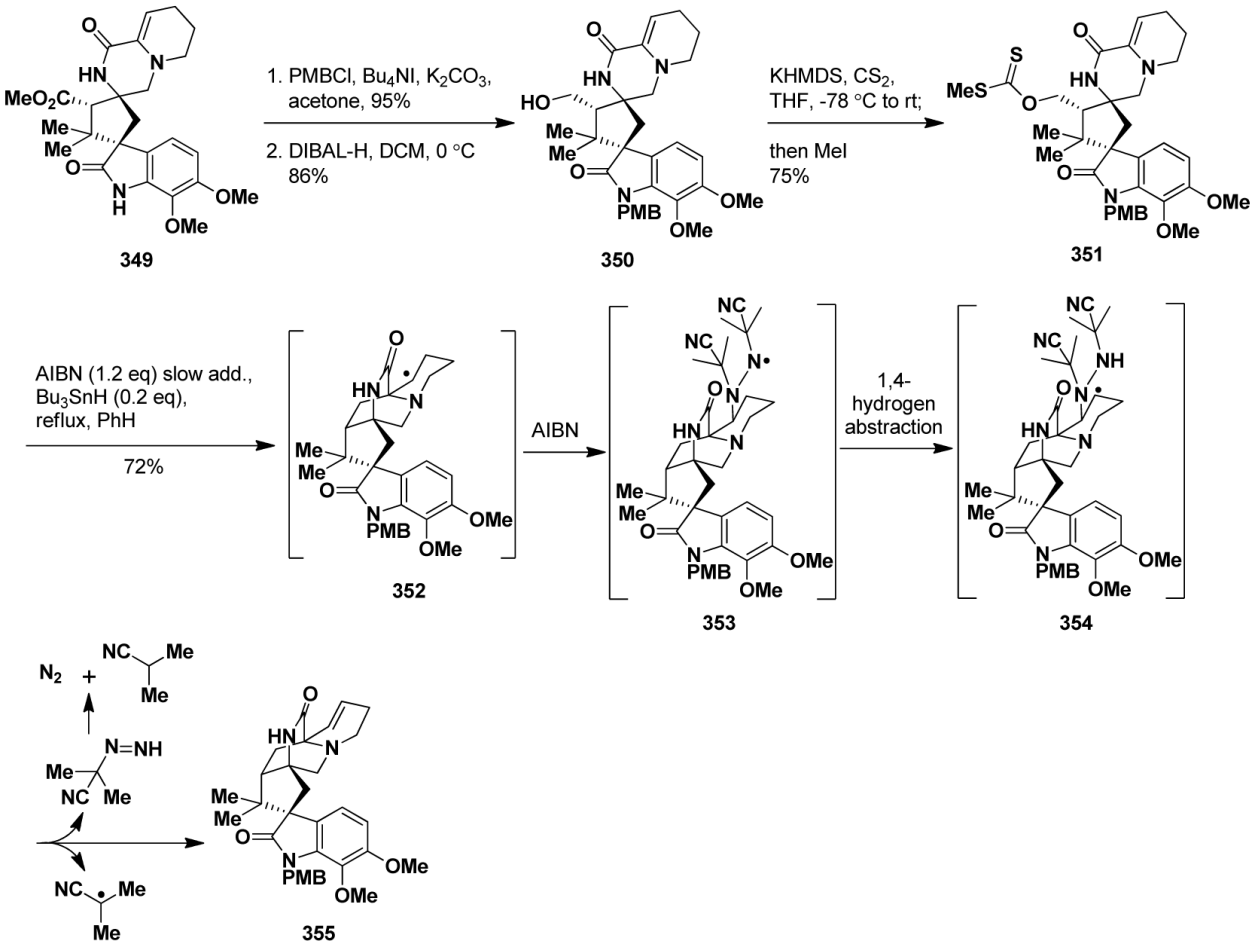
Subsequent reduction of the methyl ester with DIBAL-H proceeded smoothly in 86% yield and gave the primary alcohol **350**, which was converted to the required xanthate ester **351**; this gave the precursor for the proposed radical cyclization. Trost et al found that superstoichiometric amounts of AIBN and catalytic amounts of tributylstannane were necessary for optimum yields. The resulting nitrogen-centered radical **353** can then participate in a 1,4-hydrogen abstraction to generate alkyl radical **354**, which underwent fragmentation to the observed unsaturated product **355**, accompanied by an isobutyronitrile radical, and a monoalkyl diazene. This *oxidative* type of process under *reductive* conditions was unprecedented and resulted in the synthesis of a very useful alkene capable of further modification. For the purposes of the current synthesis, that modification was reduction, but useful analogs available by oxidation are also available that resemble other members of the family (Scheme 66).

The double bond of **355** proved to be very resistant toward attempted hydrogenation (Scheme 67). The starting material was further purified by stirring over Raney nickel to remove any sulfur catalyst poisons from the previous step. Subsequently, the reduction was possible with Crabtree's catalyst and worked best with a hydrogen pressure of 150 psi to obtain a fast and clean reaction (Scheme 67).[75] Removal of the PMB protecting group in the next step was realized using protolytic conditions, which involved stirring in trifluoroacetic acid at reflux with anisole as the scavenger, to give oxindole **356**.

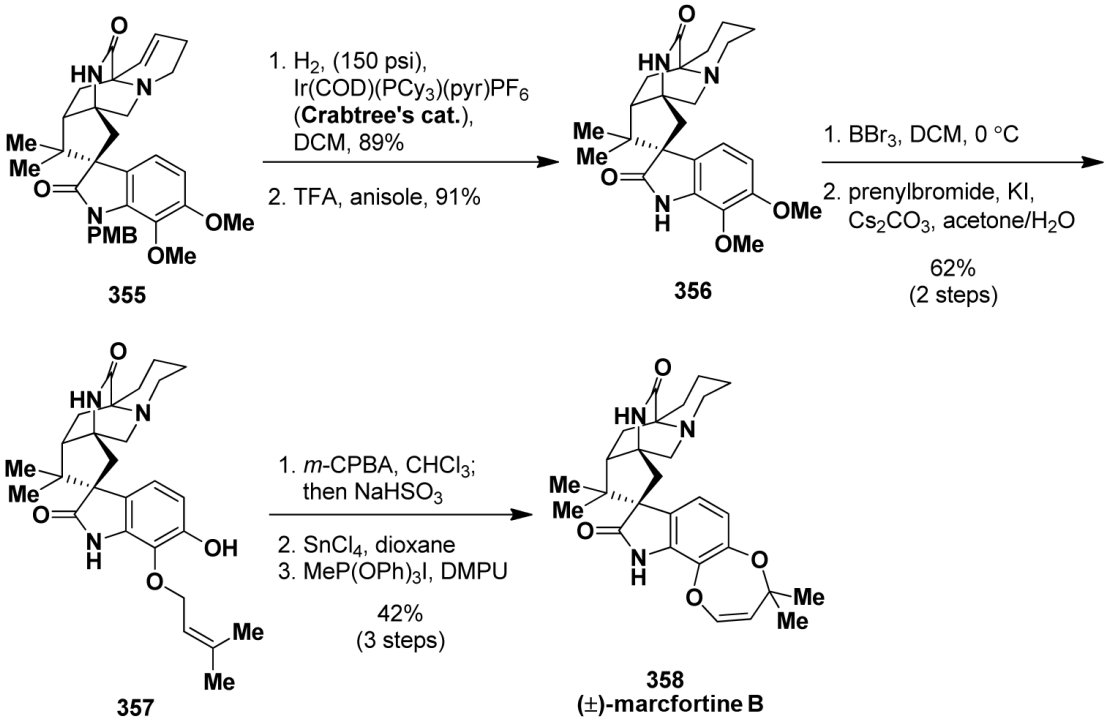
With all but the remaining dioxepin ring in place, the synthesis was completed using a known four-step protocol reported by Williams and Cushing.[76] The aryl methyl ethers were deprotected with boron tribromide, and selective



Scheme 65. Synthesis of spirooxindole intermediate **349**.



Scheme 66. Synthesis of spirooxindole lactam intermediate **355**.



Scheme 67. Synthesis of marcfortine B **358**.

monoprenylation provided intermediate **357**. After epoxidation with *m*-chloroperoxybenzoic acid, a tin tetrachloride-mediated *endo* cyclization took place, and the subsequent dehydration afforded (±)-marcfortine B **358** (Scheme 67).

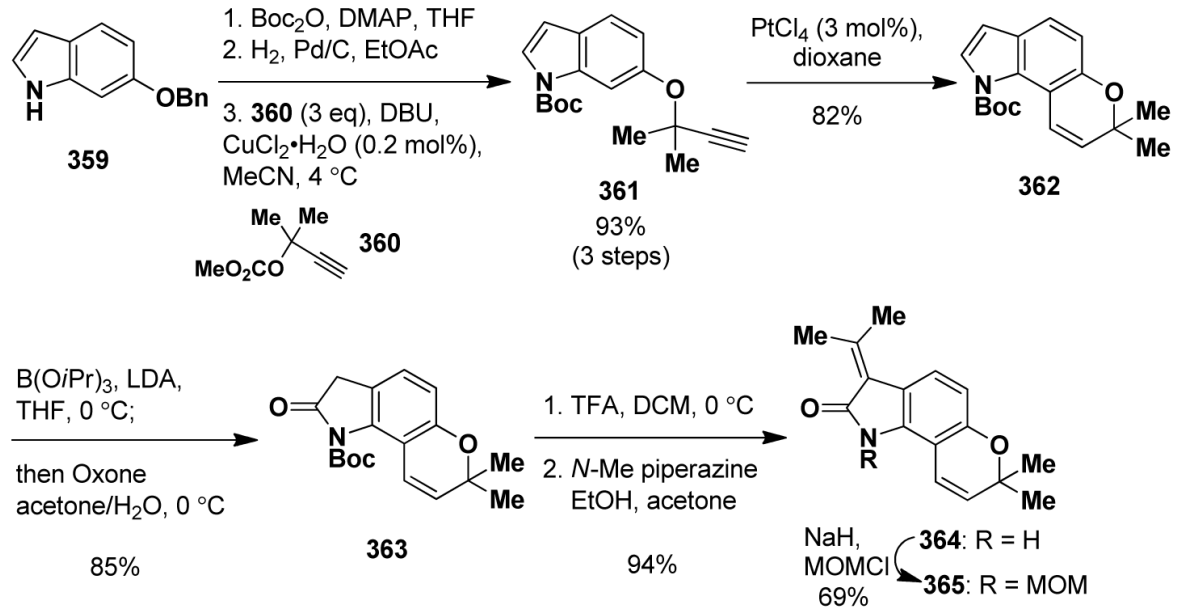
3.8.2 Synthesis of (–)-marcfortine C. Trost et al also reported the synthesis of (–)-marcfortine C **375**,[72] which started from commercially available 6-benzyloxyindole **359** using a known procedure[77] that involved Boc protection, benzyl ether hydrogenolysis, and copper-catalyzed propargylation to generate indole **361** in excellent overall yield (Scheme 68). The thermal Claisen rearrangement of **361** was known to proceed with the loss of the Boc group. On the other hand, the platinum-catalyzed methodology originally developed by Pastine et al permitted smooth formation of **362** in 82% yield.[78] Treatment of this compound with LDA in the presence of triisopropyl borate led to 2-indolylboronate, which was oxidized to yield oxindole **363** in 85% yield. At this stage, the Boc group was removed with trifluoroacetic acid, and the acetone adduct **364** was prepared by treatment with *N*-methyl piperazine. Preparation of *N*-methoxymethyl (MOM) derivative **365** was performed in good yield under standard conditions of alkylation (Scheme 68).

Combination of the application of both the trimethylenemethane (TMM) reaction (a palladium-catalyzed [3 + 2] cycloaddition of TMM with an isopropylidene oxindole) and subsequent oxidation based on isopropylidene oxindole **365** (Scheme 69) gave a 60% overall yield (on gram scale) of allylic alcohol **368** in 89% ee. Accordingly, this two-step sequence effectively set the stereochemistry at the spirocenter, which Trost et al anticipated would allow them to establish all the remaining stereocenters in (–)-marcfortine C **375** by analogy to previous work by their group.

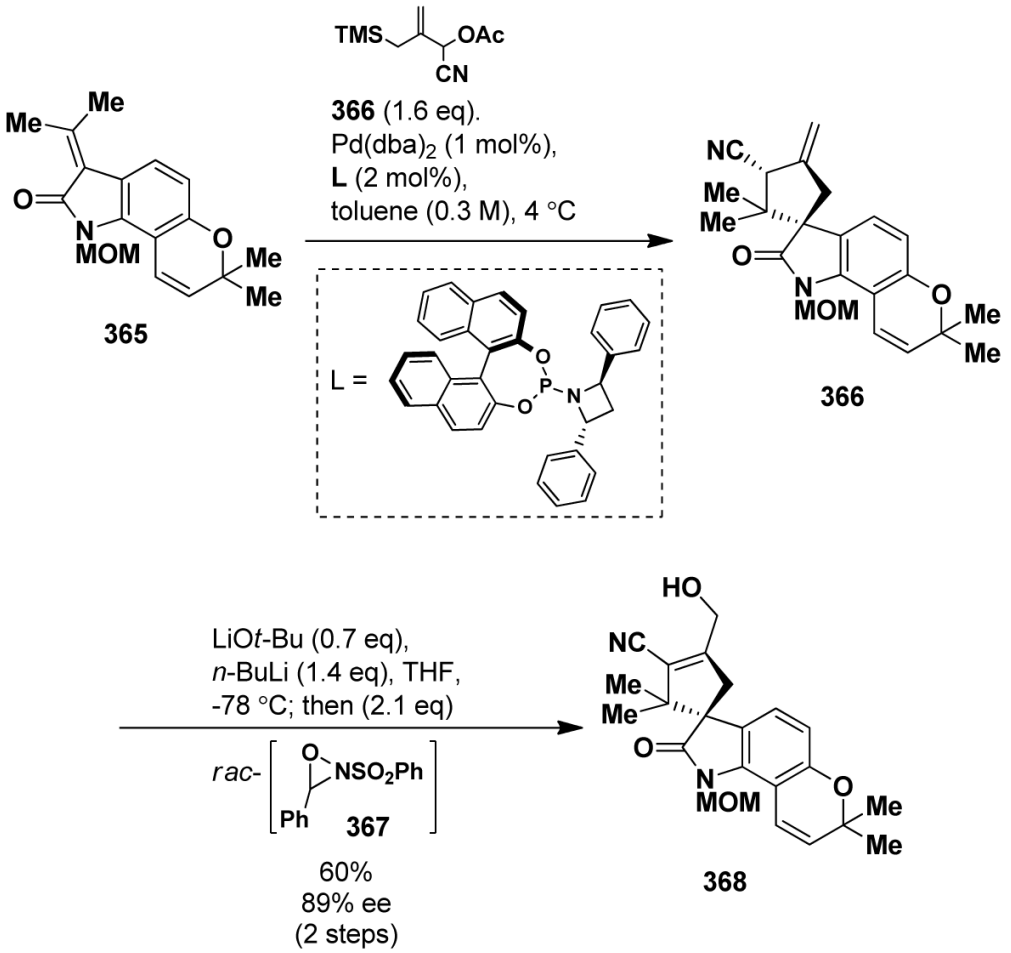
The piperidine functionality could now be readily introduced by an S_N2 alkylation, followed by elimination of the secondary alcohol to furnish **369** in 84% yield over three steps (Scheme 70). Then, primary carboxamide **369** underwent intramolecular Michael addition in the presence of 1 equivalent of *tert*-BuOLi to provide **370** in 71% yield.

With oxindole **370** in hand, Trost et al sought to effect the crucial nitrile reduction (Scheme 70). After extensive experimentation, positive results were obtained by employing triethylaluminum (as an in situ protecting group for the secondary amide) in DCM, and then, DIBAL-H was added to provide the aldehyde **371**. It was formed cleanly with a small amount of unreacted starting material. In practice, these two components were difficult to separate from each other; however, treatment of the mixture with an excess of sodium borohydride effectively reduced the aldehyde and allowed recovery of any unreacted starting material. Under these conditions, the primary alcohol **372** was obtained in 58% yield based on the recovered starting material.

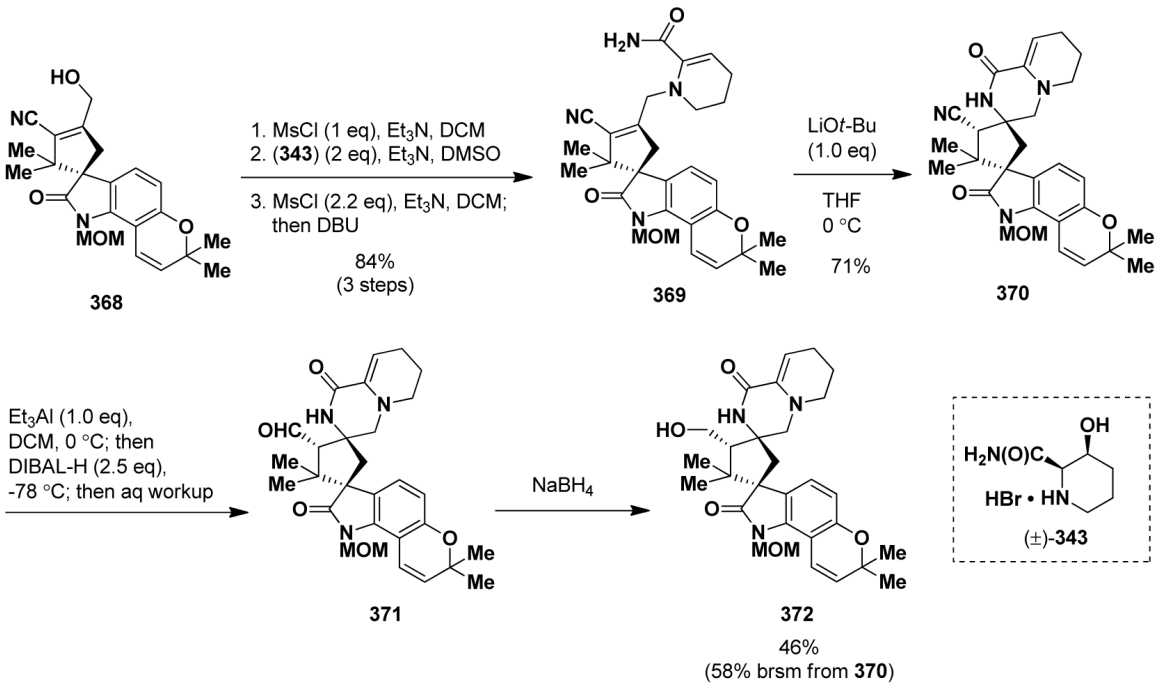
With primary alcohol (**372**) in hand, Trost et al were able to complete the synthesis of (–)-marcfortine C **375** (Scheme 71). The xanthate ester formation proceeded in 75% yield using *tert*-BuOLi as the base to give compound **373**. Importantly, at this stage, when Trost et al used an excess of *N,O*-bis(trimethylsilyl)acetamide (BSA), *n*-Bu_3SnH (0.2 equivalents), and AIBN (3.4 equivalents) with oxindole **373**, then the bicyclo[2.2.2]diazaoctane **374** was generated in around 40% yield. It was also realized that doubling the equivalents of AIBN improved the yield to 54% (the use of BSA in such radical cyclizations was unprecedented). In a number of reactions where the substrates and/or products may be subject to decomposition due to the adventitious presence



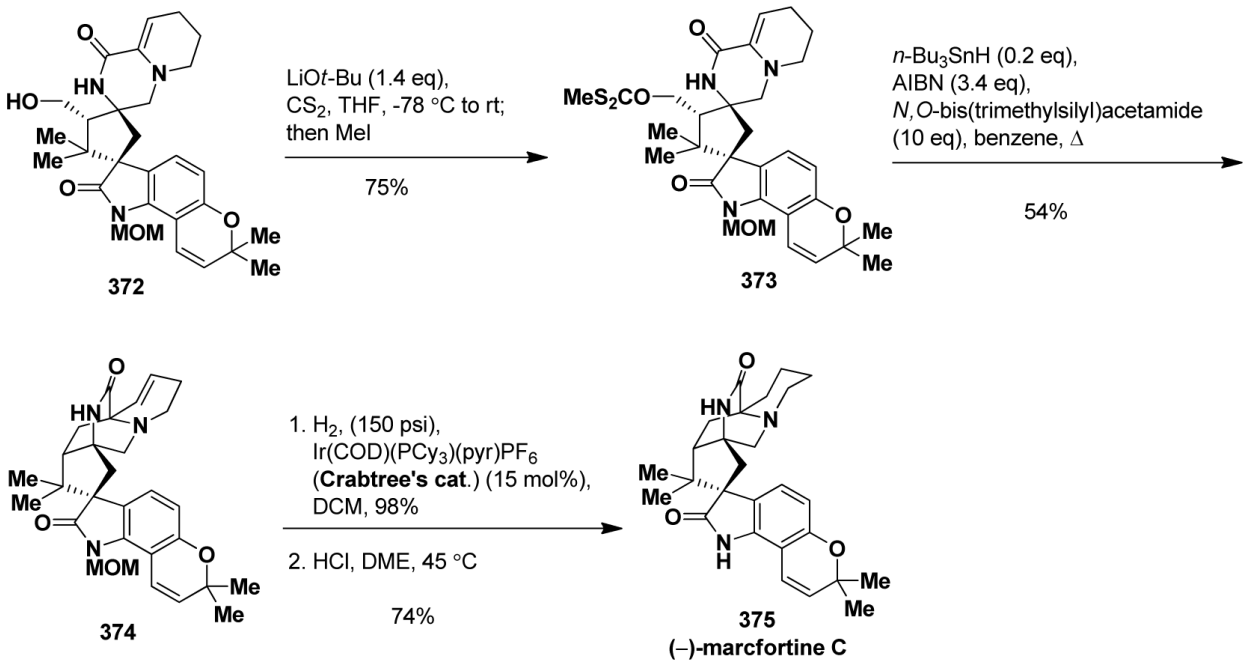
Scheme 68. Synthesis of *N*-methoxymethyl oxindole derivative **365**.



Scheme 69. Synthesis of allyl alcohol oxindole **368**.



Scheme 70. Synthesis of spirooxindole intermediate **372**.



Scheme 71. Synthesis of (–)-marcfortine C **375**.

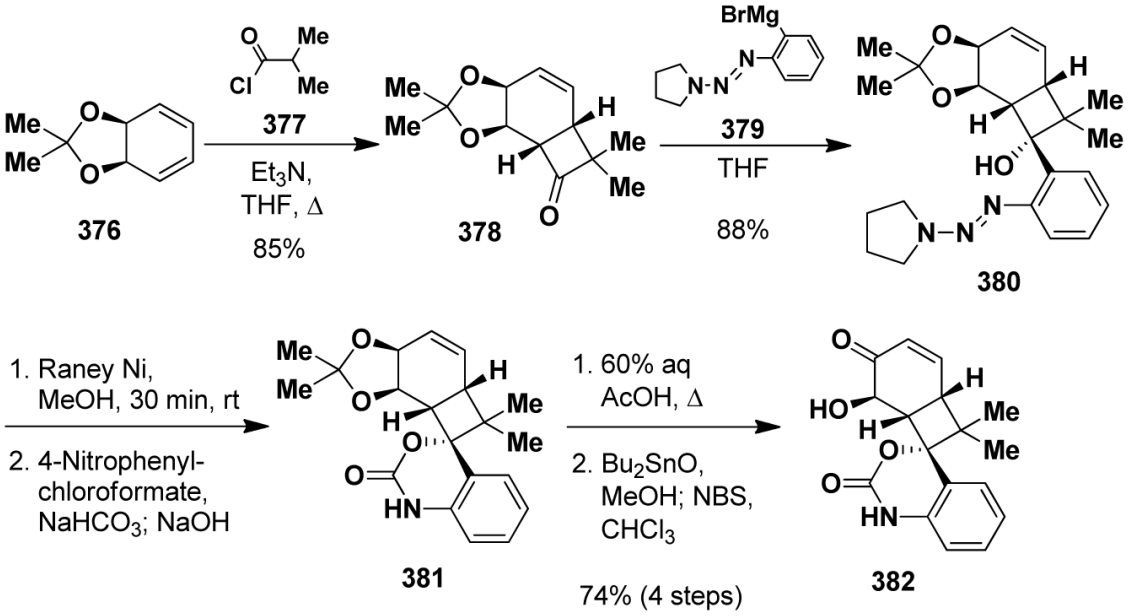
of acid or moisture, addition of BSA has proven to be an innocuous acid and moisture trap. It was suspected that it played a similar role here. On the other hand, a direct role in the radical process such as by turning over the tin catalyst by silylating the methylthio fragment could not be ruled out. As was observed earlier, the cyclization reaction proceeded in an oxidative fashion to provide the unsaturated product. Thus, it was now necessary to effect a chemoselective reduction of this newly formed olefin **374** in the presence of the chromene moiety. Notably, both olefins were part of a fused six-membered heterocycle and possessed a vicinal tertiary carbon. Initial tests using either Wilkinson's or Crabtree's catalysts were highly chemoselective and the latter proceeded in nearly quantitative yield. Finally, deprotection was achieved with aqueous HCl in DME to provide (–)-marcfortine C **375** in 74% yield.

3.9 Wood et al's total synthesis of (±)-welwitindolinone A isonitrile. An efficient and highly stereoselective total synthesis of the natural product (±)-welwitindolinone A isonitrile **401** was described by Wood et al.[79] The synthesis started with the [2 + 2] ketene cycloaddition of racemic acetonide **376** with excess isobutyryl chloride **377** and triethylamine (to form dimethylketene in situ) in refluxing THF to give ketone **378** in 85% yield as a single regio- and diastereoisomer (Scheme 72). Cyclobutanone **378** was treated with triazene-protected aryl Grignard reagent **379** to give tertiary alcohol **380** in excellent yield as a single diastereomer. Reductive deprotection of the triazene was followed by urethane formation to furnish **381**, which upon acidic hydrolysis of the acetonide and regioselective oxidation of the allylic alcohol provided hydroxy enone **382**. By use of this efficient four-step sequence, Reisman et al was able to obtain multigram quantities of enone **382** from acetonide **380** with only a single chromatographic purification.

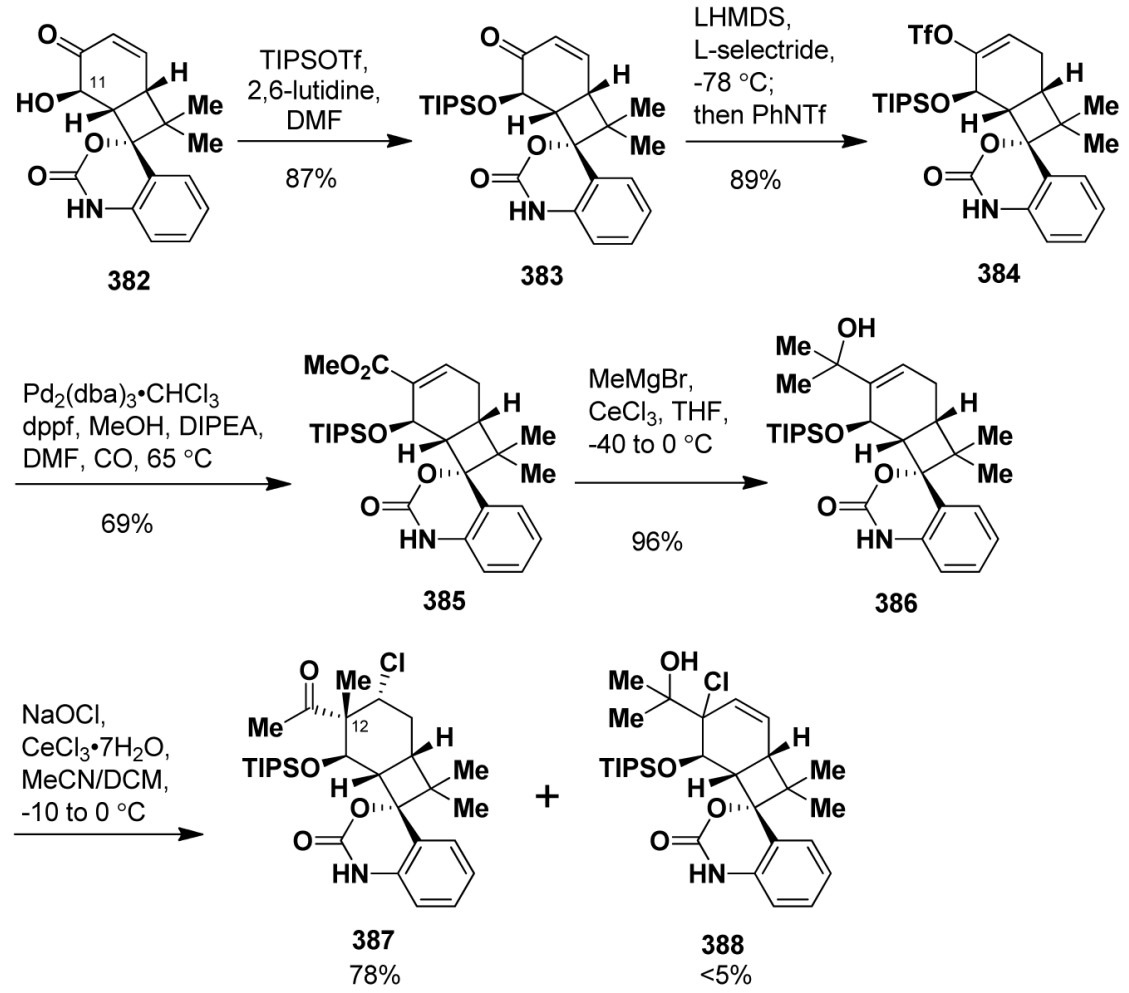
It was postulated that protection of the C-11 hydroxyl group of enone **382** with a suitably large protecting group could override the inherent facial bias of the bicyclic skeleton and promote chlorination from the concave face of the molecule. Consequently, α-hydroxy enone **382** was converted to the triisopropyl silyl ether **383** (Scheme 73). Next, tertiary allylic alcohol **388** was prepared by a sequence that began by treatment of α-siloxy ketone **383** with LHMDS (to deprotonate the urethane), and this was followed by L-selectride and then by *N*-phenyltriflimide to give enol triflate **384** in 89% yield.

The subsequent exposure of triflate **384** to $Pd_2(dba)_3$ and 1,1′-bis-(diphenylphosphino)-ferrocene (dppf) in the presence of methanol, DIPEA, and carbon monoxide furnished enoate **385** in 69% yield. When the enoate **385** was subjected to reaction with excess methyl magnesium bromide and anhydrous cerium trichloride, this process provided tertiary allylic alcohol **386**, the required semipinacol rearrangement substrate. To this end, Wood et al found that using NaOCl/AcOH as the chlorine source with $CeCl_3$ in DCM/MeCN and maintenance of the reaction temperature between –10°C and 0°C provided chloroketone **387** in 78% isolated yield as a single diastereomer (Scheme 73).

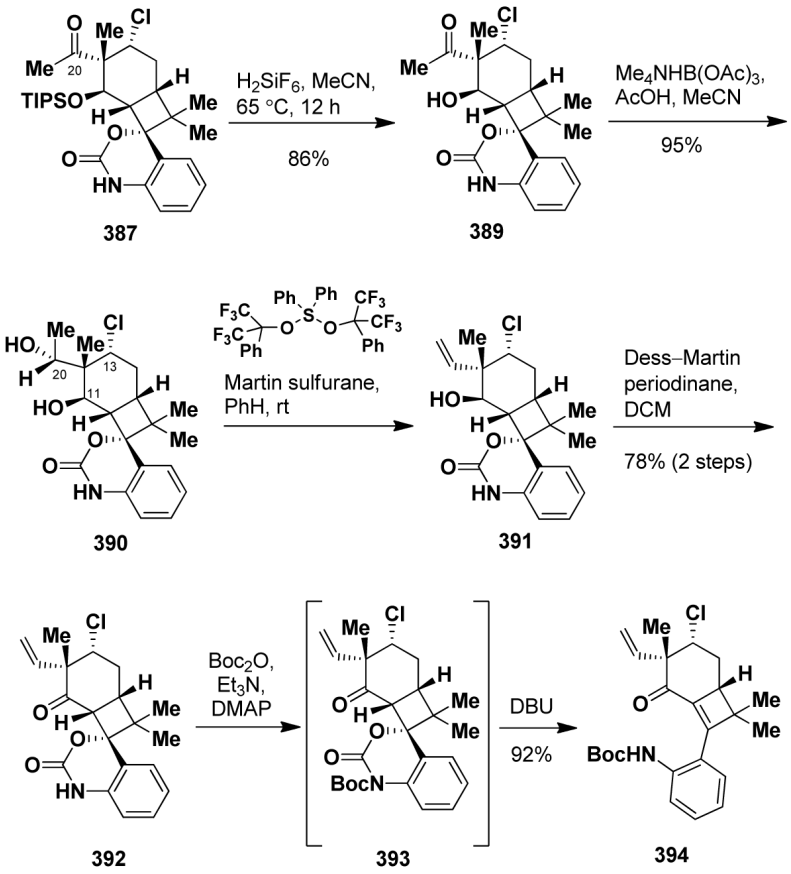
With chloroketone **387** in hand, attention turned to accessing the fully functionalized tetracyclicketone **392** (Scheme 74) by conversion of the C-20 ketone to the requisite vinyl functionality. After removal of the TIPS-protecting group with H_2SiF_6, hydroxy ketone **389** was reduced with $Me_4NHB(OAc)_3$ to give diol **390** in 82% overall yield (Scheme 74).



Scheme 72. Synthesis of hydroxy enone **382**.



Scheme 73. Synthesis of chloroketone **387**.



Scheme 74. Synthesis of enone **394**.

Exposure of diol **390** to Martin's sulfurane resulted in regioselective dehydration of the C-20 alcohol,[80] to furnish the required vinyl moiety of the final target molecule.

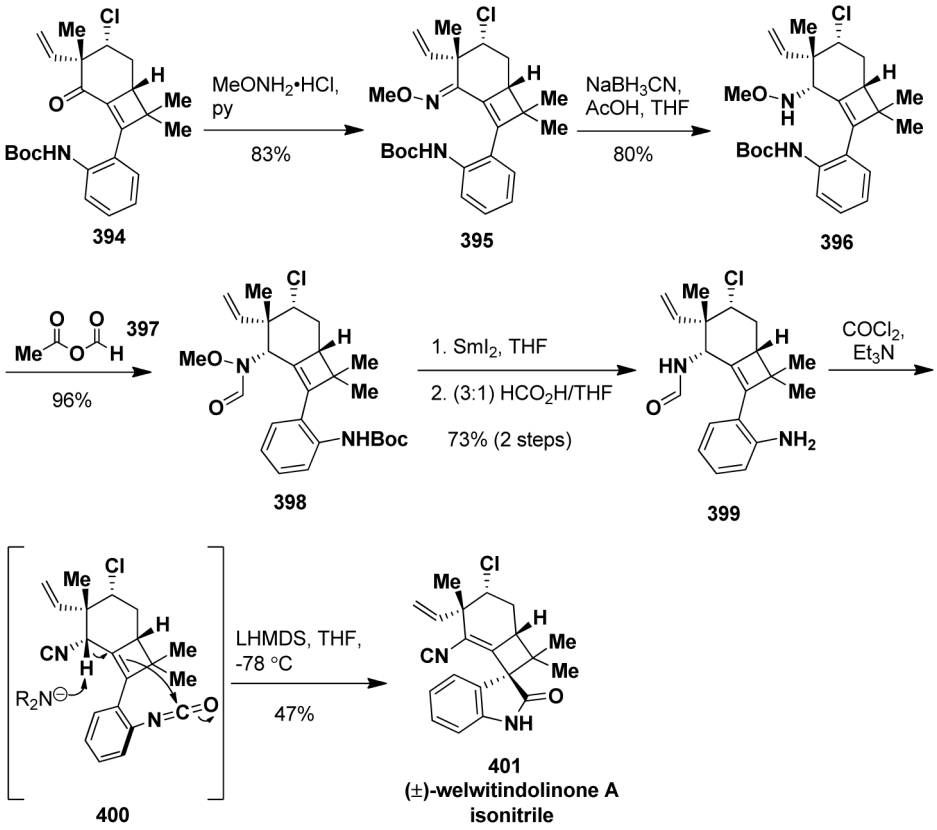
The subsequent oxidation of alcohol **391** using Dess–Martin periodinane furnished ketone **392** in 78% yield over two steps. The conversion of the carbamate **392** to the *N*-Boc-imide **393**, followed by in situ treatment with DBU at room temperature, delivered *N*-Bocaniline **394** in 92% yield (Scheme 74).

In the last stages of the synthesis, advancement of enone **394** to the corresponding methyl oxime **395**, followed by exposure to reducing conditions, $NaBH_3CN$/AcOH, resulted in the formation of methoxylamine **396** (Scheme 75). Subsequent formylation of the latter with acetic formic anhydride (AFA) provided a near quantitative yield of methoxyamide **398**, which, upon sequential exposure to SmI_2 followed by formic acid, underwent N-O bond cleavage and Boc-deprotection to furnish aniline **399**.[81]

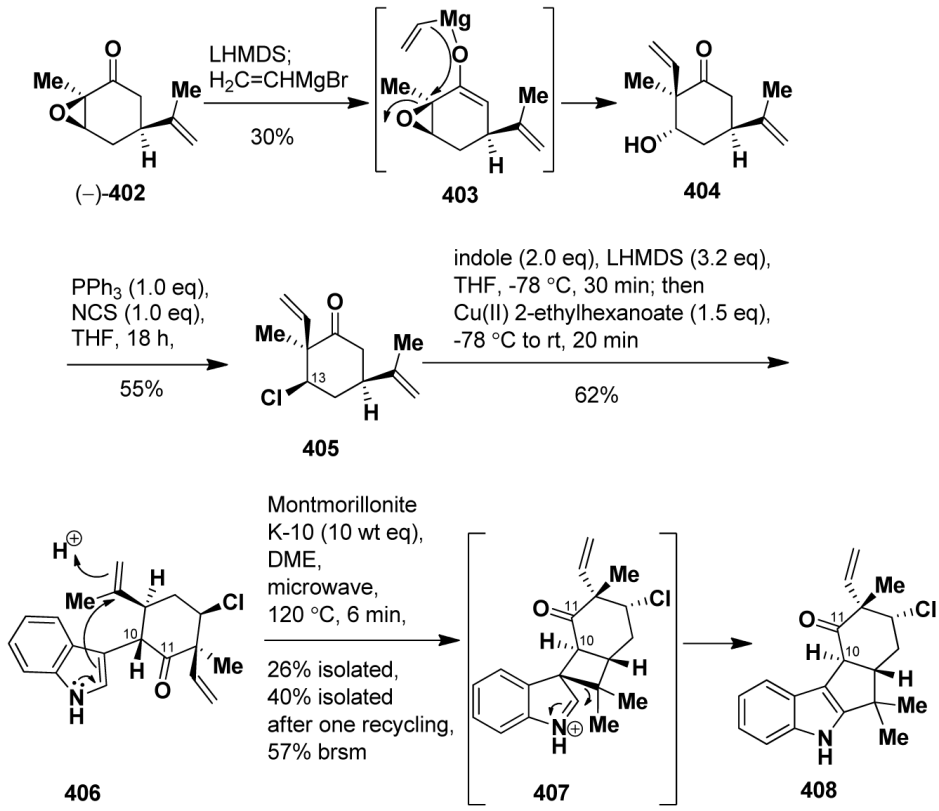
In the final ring-closing event, treatment of formamide **399** with excess phosgene and triethylamine promoted simultaneous dehydration of the formamide to the isocyanide and conversion of the aniline to the isocyanate to deliver isocyanoisocyanate **400** (Scheme 75).

Upon removal of the triethylamine salts by filtration and drying in vacuo, it was found that treatment of **400** with excess LHMDS at –78°C provided the final target alkaloid **401** in 47% yield.[82] However, attempts to further optimize the reaction by changing the base or rigorously drying the intermediate isocyano/isocyanate **400** did not significantly improve the yield of **401** (Scheme 75).

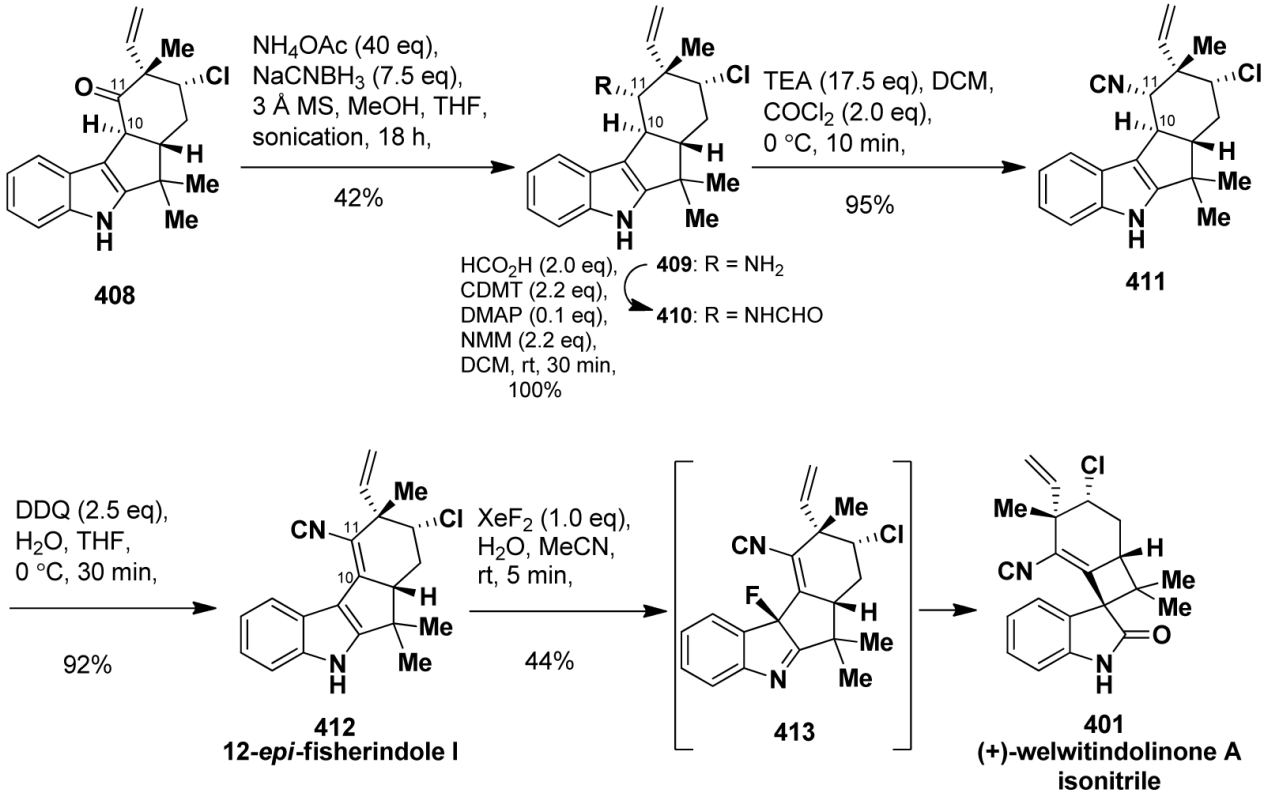
3.10 Baran et al's enantiospecific total synthesis of welwitindolinone A isonitrile. In 2008, Baran et al published the enantiospecific total synthesis of (+)-welwitindolinone A isonitrile **401** via a redox economic approach.[54] Initially, carvone oxide **402** (obtained from (*S*)-carvone, Scheme 76) was examined as a starting point for the production of chloroketone **405**. After several failed attempts to generate the desired chloroketone **405**, a successful route was finally developed by Baran's group inspired by a reaction developed in the Wender laboratory.[83] In Wender et al's study, α-epoxyketones were first treated with a strong base to form the corresponding enolate. Nucleophilic addition of an organometallic reagent (usually a Grignard reagent) to this epoxyenolate at the α-carbon (as opposed to the usual β-attack) formed the corresponding α-alkyl-β-hydroxy ketone. However, a quaternary carbon installation during the course of this reaction was unprecedented. Despite this potential limitation, the reaction was attempted on carvone oxide to provide ketone **404** in about 30% yield (Scheme 76). Extensive optimization efforts (solvent, nucleophile, base, additives, temperature, and



Scheme 75. Synthesis of welwitindolinone A isonitrile **401**.



Scheme 76. Synthesis of ketone **408**.



Scheme 77. Synthesis of (+)-welwitindolinone A isonitrile **401**.

addition rates) did not result in significant improvement in the overall efficiency of the reaction. Nevertheless, with alcohol **404** available, the chlorination was accomplished (NCS/PPh_3) in acceptable yield to provide the key chloroketone **405**. Despite the modest overall yield of this two-step sequence, it was used to rapidly prepare multigram quantities of **405** and was, therefore, deemed as an acceptable solution to this problem by Baran et al, especially given the difficulties in preparing **405** via other groups.[54] With chloroketone **405** in hand, the stage was set to invoke the key direct indole coupling reaction that proceeded smoothly to provide the coupled product **406** in 62% yield as a single diastereomer. Several aspects of this particular coupling are noteworthy. First, it was remarkable that chloride elimination was not observed during the course of this coupling. Second, it was discovered that, as the reaction concentration was increased, the yield improved. Third, any C-13 diastereomer of **405** present in the reaction mixture did not participate in the coupling reaction and rather suffered elimination, presumably due to the axial disposition of the chlorine atom. Finally, this effective method for direct C-C bond formation enabled all the necessary carbon atoms of these complex natural products to be secured in only three steps and was routinely carried out on multigram scale (Scheme 76).

Functional group manipulations were all that remained to complete the synthesis of (+)-**401**. In the next particular cyclization reaction, the olefin moiety at C-9 in **406** could be protonated to give a tertiary carbocation, which was intercepted by the indole ring to give intermediate **407**, which in turn led to the desired product **408**. It was found by Baran's group that montmorillonite K-10 acidic clay, with microwave irradiation, provided the desired product **408** without formation of several undesired byproducts,[54] although recycling of unreacted starting material was required (Scheme 76).

Amine **409** was obtained after performing a reductive amination protocol on ketone **408**, as shown in Scheme 77. Next, amine **409** was formylated in quantitative yield to give **410**. It was subsequently discovered by Baran et al that initial dehydration of formamide provided isonitrile **411** in 95% yield. Treatment of this compound with DDQ[83] provided 12-*epi*-fischerindole I **412** in 92% yield, which permitted access to large quantities of this natural product.[84] A mild method to accomplish the transformation of indole **412** into its corresponding oxindole was developed by Baran et al, in which **412** was treated with a solution of XeF_2 in wet acetonitrile to provide **401** in 44% yield, via the intermediacy of fluoroindoline **413**.[85] The chemoselectivity of this reagent was noteworthy, given the presence of an olefin in **412**, which is known to react with XeF2,[86] and the reactive isonitrile moiety (Scheme 77). This reaction was routinely performed on more than 50 mg of **412**, and more than 580 mg of the natural product has been prepared to date.[87]

4 Summary

In the above sections, the latest total syntheses of complex natural oxindole alkaloids are described in such a way that

the reader has access to the bioactive target molecules being studied and the latest methods used by the synthetic chemists. The syntheses were selected based on the elegant, efficient manner that solved key synthetic issues and the structural complexity presented by the oxindole alkaloids. This review is a comprehensive literature recapitulation for those chemists interested in knowing the latest improvements in the field of oxindole alkaloid total synthesis.

Author Contributions

Wrote the first draft of the manuscript: GOF. Contributed to the writing of the manuscript: JMC. Made critical revisions and approved the final version: JMC. All the authors reviewed and approved the final manuscript.

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