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SYNTHESIS OF ALKALOIDS USING RADICAL CYCLIZATIONS

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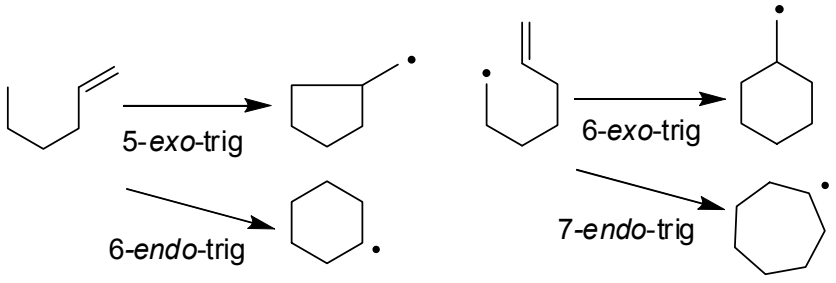
Abstract – This review focuses on radical cyclizations for the synthesis of a variety of alkaloids. Emphasis has been placed on radical cascades that afford synthesis of (−)-cephalotaxine and (±)-stemonamide.

WHAT ARE RADICALS?

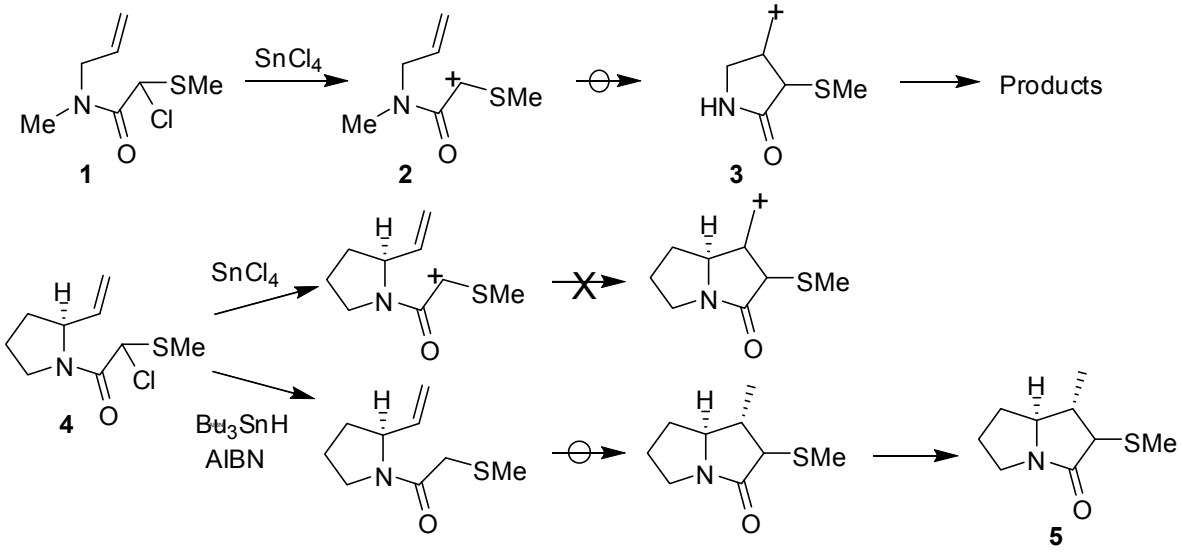
Radicals are highly reactive atoms, molecules, or ions bearing an unpaired electron and are important in fields of organic chemistry including polymer chemistry, material chemistry and electrochemistry as well as life science. Radical chemistry has been an accepted area of research for almost 110 years and its chemistry dates back to 1900, when Gomberg investigated the formation and reactions of the triphenylmethyl radical.

Radical cyclizations are reactions of a radical with one π–orbital of an unsaturated bond such as C-C double bond and serve for the construction of cyclic compounds.[1] Two types, *exo* and *endo* modes, exist for radical cyclizations. The most popular one is the 5-exo-trig mode of cyclization (Scheme 1).



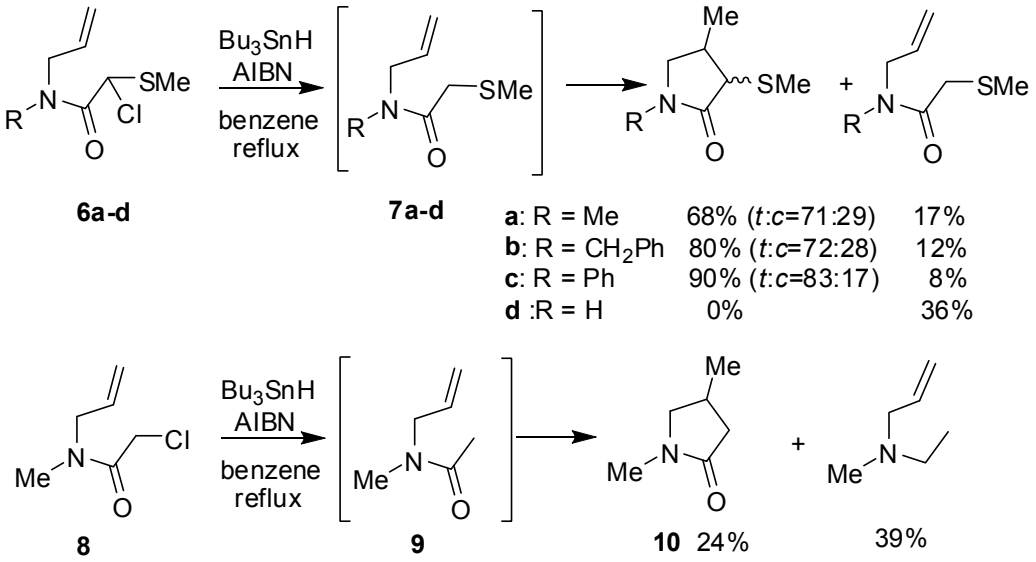
Scheme 1

In the course of our studies on olefin cyclizations of sulfur-substituted carbocations, we found that the cation **2**, generated formally from **1**, underwent olefin cyclization to give products via cyclized intermediate **3**[2] but that the compound **4** by treated with the same Lewis acid ($SnCl_4$) gave no cyclized compound. In contrast, when compound **4** was treated with Bu_3SnH in the presence of AIBN, it underwent cyclization smoothly to give product **5** (Scheme 2).[3]



Scheme 2

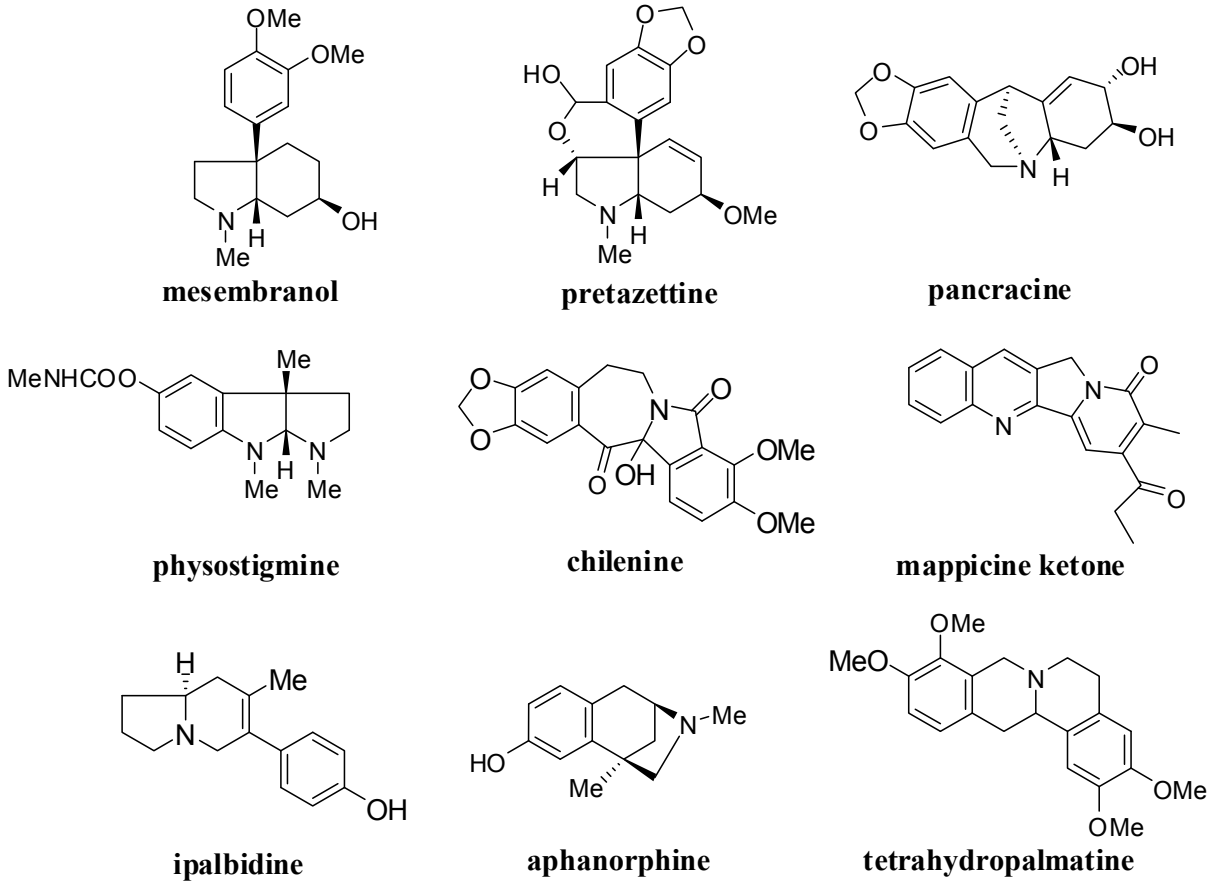
These types of carbamoylmethyl radicals, generated from the corresponding α-halogenated acetamides, had not been described in the literature and the only reported examples were Pd-catalyzed cyclizations of α–haloacetamides.[4] Reactions of **6** and **8** with Bu_3SnH/AIBN are summarized in Scheme 3.[5]



Scheme 3

The results indicate that methylthio-substituted radicals **7a-c** (R = Me, CH_2Ph or Ph) preferentially gave cyclization products, whereas the radical **9** gave only a small quantity of the cyclization product **10**. Treatment of **9** under the cyclization conditions preferentially gave the reduction product (compare **7a** and **9**). These results are somewhat surprising considering the general observation of so-called 'stabilized' radicals being less reactive than 'non-stabilized' radicals towards C-C bond-forming reactions with unsaturated bonds,[6] since radicals **7a-c** are stabilized by a captodative effect.[7] The next matter is also intriguing. Treatment of **6d** with Bu_3SnH gave only the reduction product instead of the cyclization product. This is probably a similar reason for the difficulty in obtaining γ-lactone using radical cyclization from a compound in which NH is substituted with oxygen (O).[8]

A variety of alkaloids, mesembranol,[9] pretazettine,[10] pancracine,[11] physostigmine,[12] chilenine,[13] mappicine ketone,[14] ipalbidine,[15] aphanorphine,[16] and tetrahydropalmatine,[17] were synthesized using 5-exo-trig and 6-exo-trig cyclizations of a carbamoylmethyl radical and aryl radical (Scheme 4).

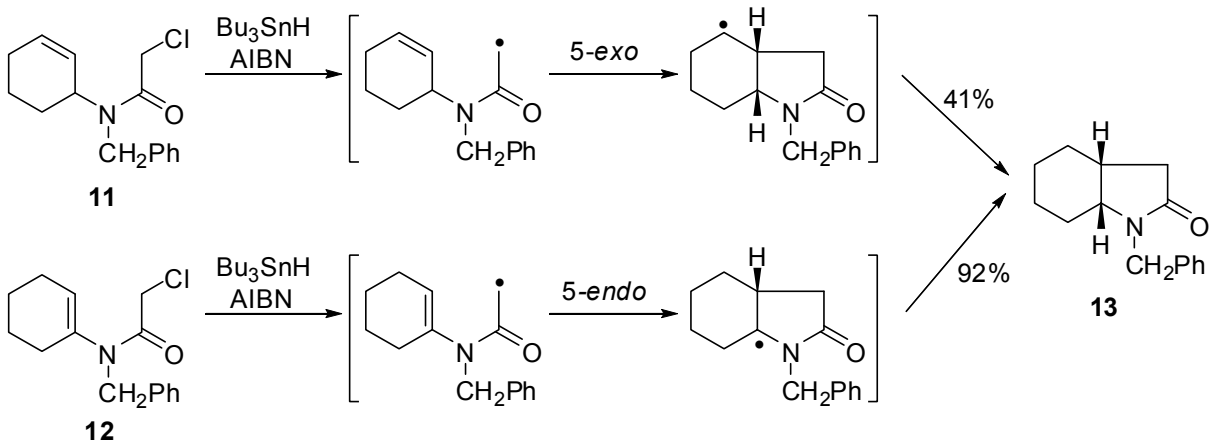


Scheme 4

5-ENDO-TRIG AND 4-EXO-TRIG CYCLIZATIONS

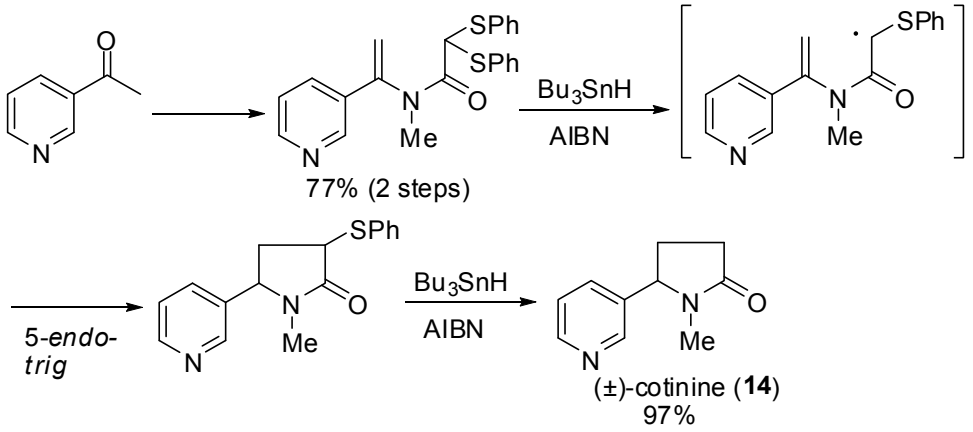
Bn_3SnH-Mediated radical cyclization of **11** gave bicyclic γ-lactam **13**. Compound **12** also

gave γ-lactam **13**.[18] Formation of **13** from **11** was a 5-exo-trig radical cyclization, which is very easy to undergo. The latter was a 5-endo-trig type cyclization, which is recognized to be very difficult to undergo (Scheme 5).[19]



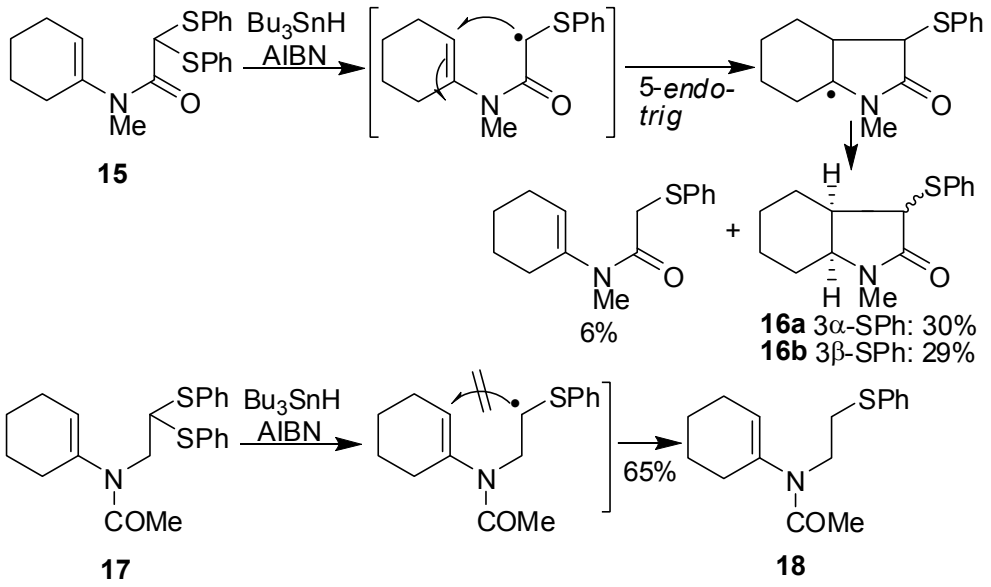
Scheme 5

5-Endo-trig cyclization was useful for the synthesis of β-non-substituted γ-lactams, and the synthesis of (±)-cotinine (**14**) is illustrated in Scheme 6.[20]



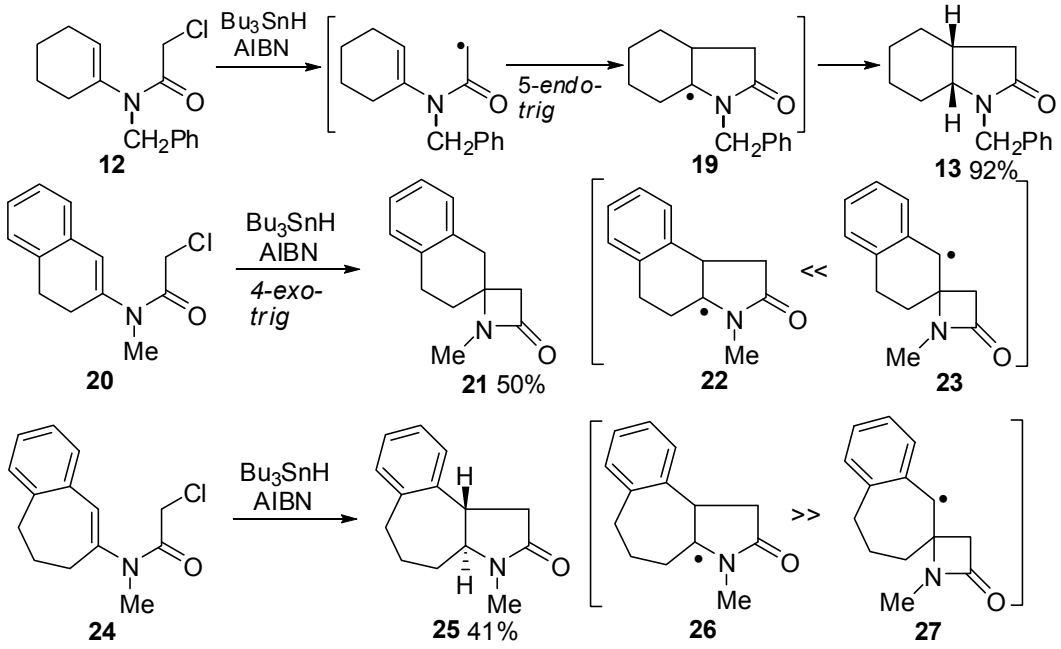
Scheme 6

In order to examine the effect of the carbonyl group in the enamide **12** for the success of 5-endo-trig cyclization, we examined the reaction of enamide **15** (Scheme 7). Treatment of **15** with Bu_3SnH in the presence of AIBN gave the 5-endo-trig cyclization product **16a,b** and the reduction product. However, the positional isomer **17** gave only the reduction product **18** when treated with Bu_3SnH and AIBN. No 5-endo-trig cyclization product was isolated. Thus, it was shown that the carbonyl group incorporated into the five-membered ring is essential for effecting the 5-endo-trig cyclization, though the exact role of the carbonyl group is obscure at present.



Scheme 7

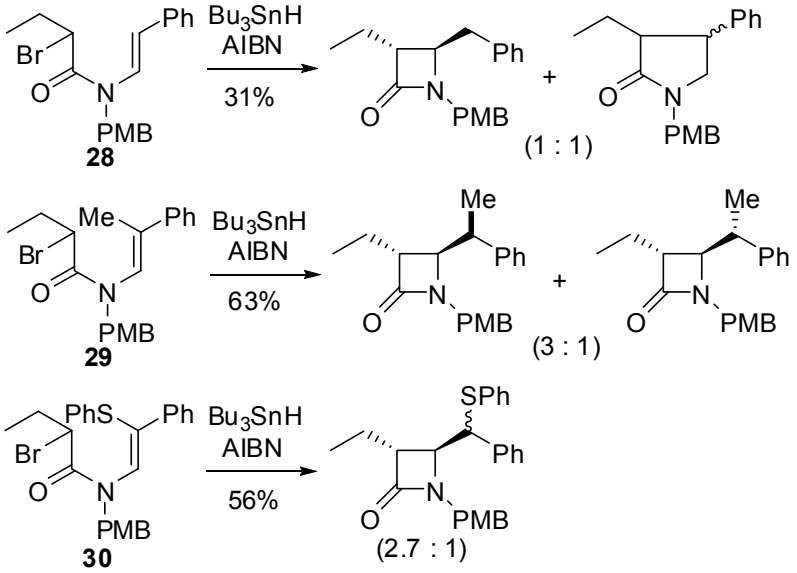
During the study on 5-endo-trig cyclizations of carbamoylmethyl radicals, we found that the cyclization of enamide **20** afforded the tricyclic β-lactam **21** (Scheme 8).[18] No γ-lactam was detected in the reaction mixture. The difference in the mode of cyclization between enamides **12** and **20** may be explained in terms of the electronic stability between the radical intermediates **19** and **23**, generated by a ring closure of the corresponding carbamoylmethyl radical. The exclusive formation of the β-lactam **21** from **20** suggests that the benzylic radical intermediate **23** might be more stable than the α–acylamino radical **22** which affords γ-lactam.



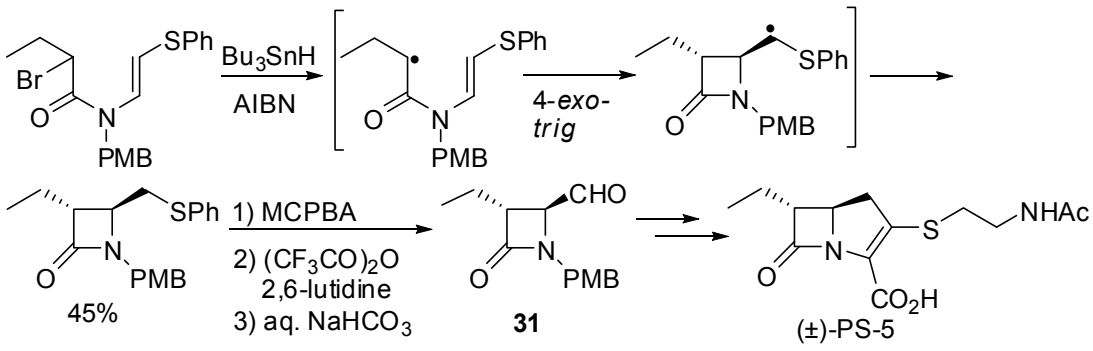
Scheme 8

Inspection of molecular models indicates that the radical intermediate **23** should be stabilized due to excellent overlapping of the p-orbital of the radical center with the neighboring aromatic π-system.[18] In sharp contrast to the case of **20**, which gave only the β-lactam **21**, enamide **24** provided the γ-lactam **25**. No β-lactam-like compound was isolated. Molecular models indicate that the p-orbital of the seven-membered benzylic radical **27** is almost perpendicular to the neighboring aromatic π-system in its most conformationally stable form, so that the α-acylamino radical **26** was relatively stable in preference to the benzylic radical **27**, leading to the observed γ-lactam **25**.[18]

Synthesis of monobactam was then examined. We found that the phenyl group alone was insufficient to stabilize the radical intermediate such as **23** (Scheme 9) formed by 4-exo-trig cyclization of bromide **28**.[21] The methyl or phenylthio group (see **29** or **30**) as an additional radical stabilizing group gave exclusively β-lactam.[22] The phenylthio group alone provided β-lactam.[23] Preparation of synthetic intermediate (**31**) for （±)-PS-5 is illustrated in Scheme 10.[23]



Scheme 9

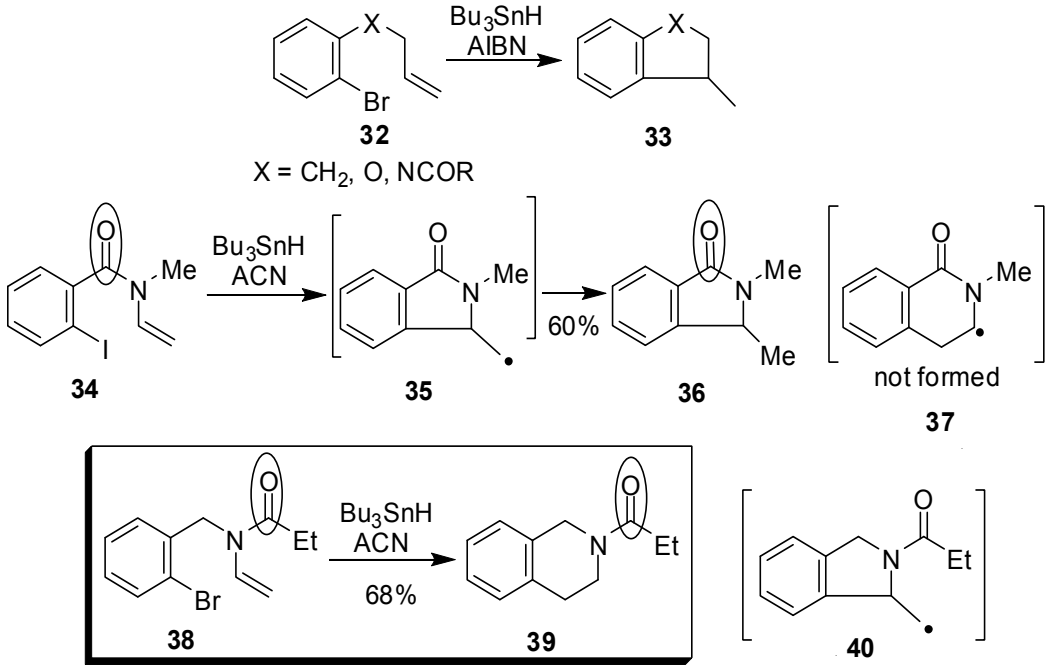


Scheme 10

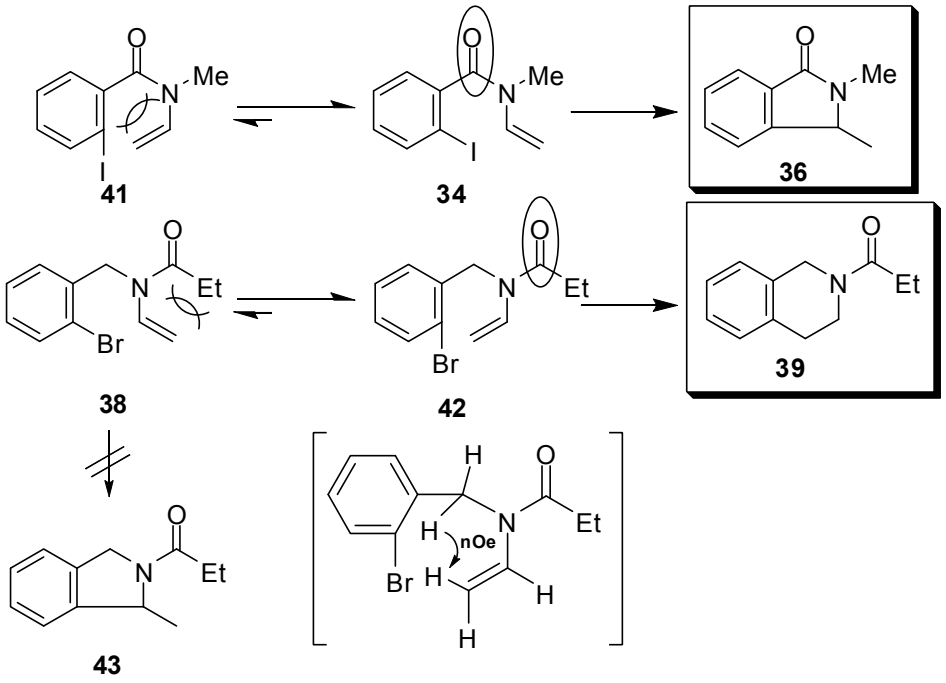
ARYL RADICAL CYCLIZATION ONTO ENAMIDE OLEFINS: 6-ENDO-SELEVTIVE CYCLIZATIONS

A 5-exo-trig cyclization is generally preferred over a 6-endo-trig ring closure in systems having an alkenic bond at the 5-position relative to the aryl radical center. For example, aryl bromides **32** (X = CH_2, O, NCOR) (Scheme 11), upon treatment with Bu_3SnH/AIBN, gave almost exclusively the 5-exo cyclization products **33**. This is also the case for the cyclization of enamide **34**, which gave only the five-membered lactam **36** via the radical intermediate **35** by 5-exo cyclization, though the reaction is expected to give more stable α–acylamino radical **37** by 6-endo cyclization. However, we found that the bromide **38** underwent an aryl radical cyclization in a 6-endo-trig manner to give exclusively six-membered lactam **39**.[24] The possibility of a consecutive 5-exo cyclization and neophyl-like rearrangement of the resulting radical **40** could be ruled out by the effect of various Bu_3SnH concentrations addition times and reaction temperatures.[25]

The most plausible explanation for the results with **34** and **38** may be derived from consideration of the rotation of the enamide. In the conformers **41** (for **34**) and **38** (for **42**), severe steric repulsions between acyl and C=C groups, respectively, are evident (Scheme 12). The conformers **34** and **42**, therefore, predominate, and the resulting radicals attack on the more proximate C_α-position of **34** and C_β-position of **42** to give the observed 5-exo cyclization product **36** and the 6-endo cyclization product **39**, respectively. NOE difference spectroscopy also indicated that compound **38** exists only in the conformer **42**.



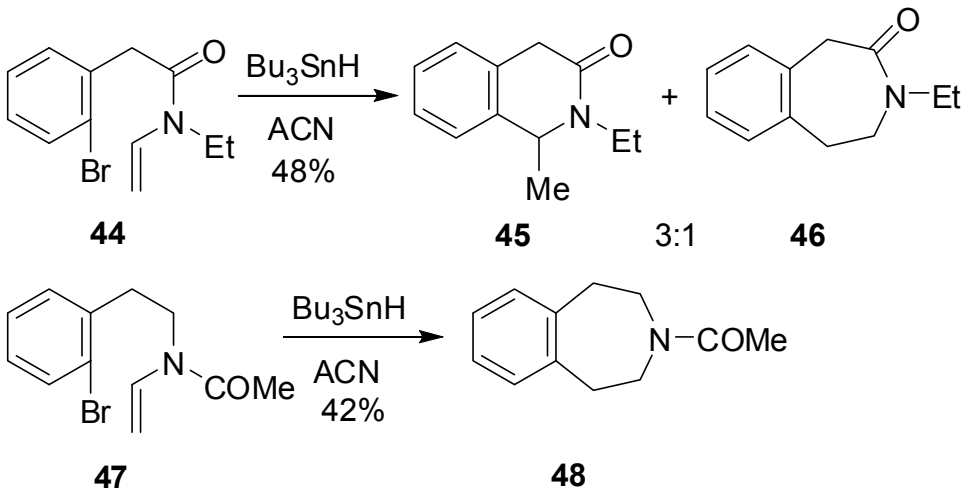
Scheme 11



Scheme 12

7-ENDO-SELECTIVE CYCLIZATIONS

We next examined the modes of cyclization of compounds **44** and **47** (Scheme 13). When enamide **44** was treated with Bu_3SnH in the presence of ACN (1,1'-azobiscyclohexanecarbonitrile), a 3:1 mixture of **45** and **46** was obtained. Formation of **45** and **46** may be explained simply by 6-*exo*-trig and 7-endo-trig cyclizations of the aryl radical formed from **44**, respectively. On the other hand, a similar cyclization of enamide **47** gave the seven-membered compound **48**. An *exo* mode of cyclization also could be shifted to an *endo* mode by a positional change of the carbonyl group of enamide.



Scheme 13

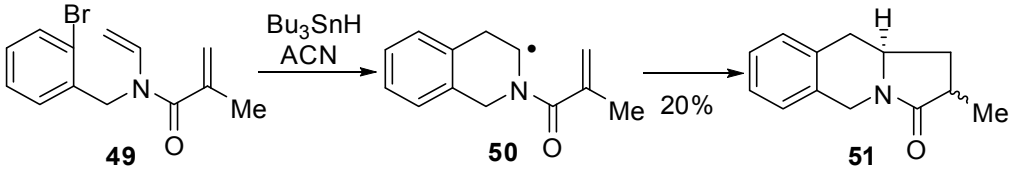
RADICAL CASCADE

A radical generated by the first radical cyclization can cause the second cyclization with another radical acceptor in the same molecule. This consecutive radical cyclization is called "radical cascade" or "tandem radical cyclization". This reaction serves as a method for construction of polycyclic systems of natural products.

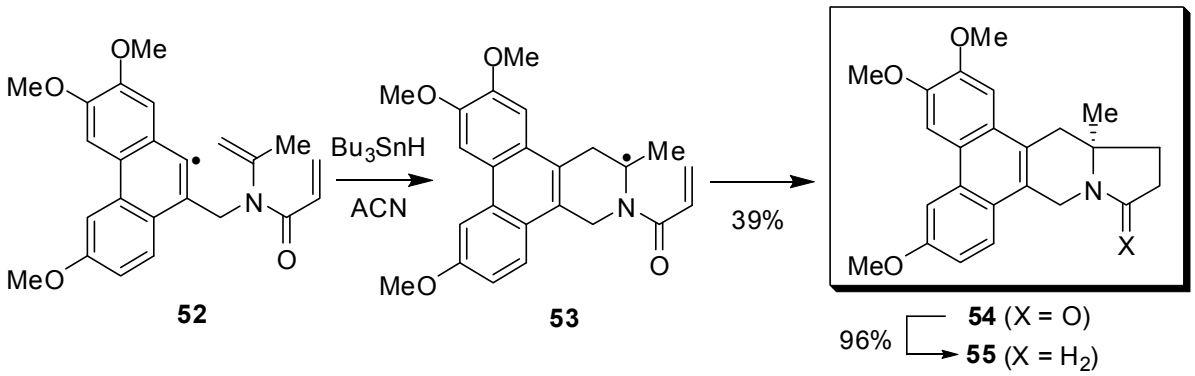
6-*ENDO*-TRIG/5-*ENDO-TRIG* RADICAL CASCADE

Synthesis of 13a-Methylphenanthroindolizidines.

When compound **49** (Scheme 14) was treated with Bu_3SnH in the presence of ACN, the tricyclic compound **51** was obtained. Formation of **51** was rationalized in terms of 6-*endo*-trig cyclization of the aryl radical formed from **49** followed by 5-*endo*-trig cyclization of the resultant intermediacy of α-amidoyl radical **50**. The present method was applied to the synthesis of 13a-methylphenanthroindolizidine alkaloids such as **55** from **52** (Scheme 15).[26] It should be noted that 5-*endo*-trig cyclization did not occur in the absence of the carbonyl group in **50** or **53**.



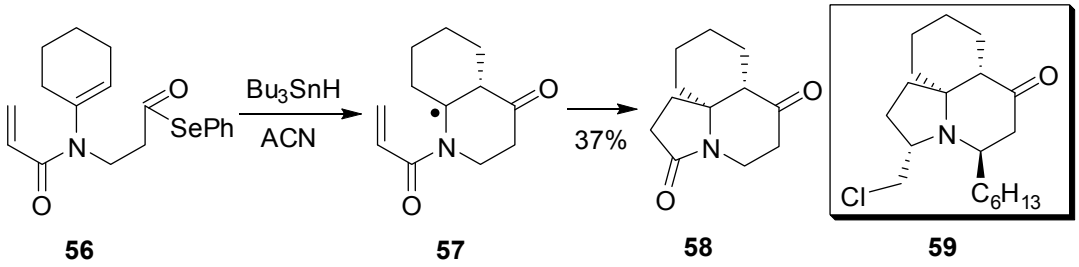
Scheme 14



Scheme 15

Synthesis of Cylindricine Skeletons

Compound **56**, on treatment with Bu_3SnH/ACN, afforded tricyclic compound **58** via α-amidoyl radical **57** (Scheme 16).[27] The structure of **58** was unequivocally established by X-ray crystallographic analysis. Compound **58** is a basic structural element of the anti-cancer agent cylindricine A (**59**).

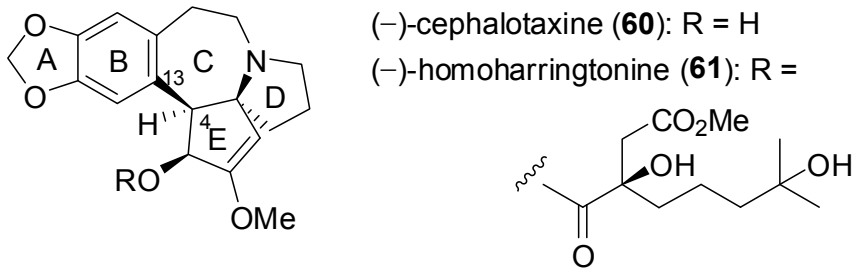


Scheme 16

7-ENDO-TRIG/5-ENDO-TRIG RADICAL CASCADE

Synthesis of (−)-Cephalotaxine

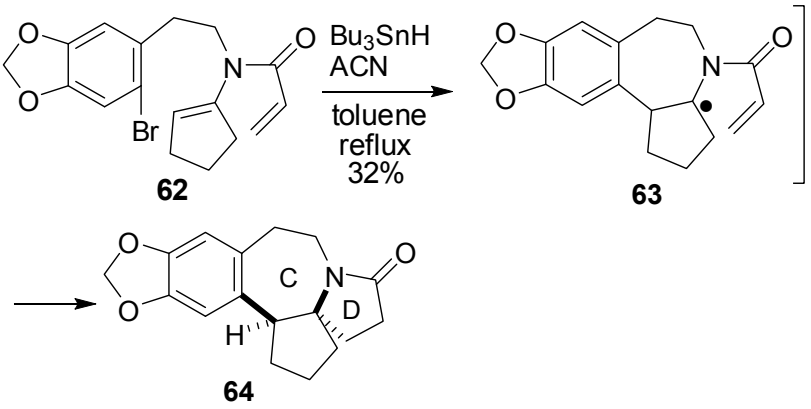
Cephalotaxus alkaloids are a class of cytotoxic natural products first isolated from Asian plum yews *Cephalotaxus drupacea* and *Cephalotaxus fortunei*. (—)-Cephalotaxine (**60**) has attracted much attention due to its fascinating pentacyclic structure and the antileukemic activity of its ester derivatives such as homoharringtonine (**61**) (Scheme 17). Since the first total synthesis of (±)-cephalotaxine by Weinreb and Semmelhack, a number of approaches to the synthesis of (—)-cephalotaxine (**60**) have been reported and several efforts have culminated in a total synthesis of a racemic mixture of or optically active cephalotaxine. One of the most frequently used strategies is C_4-C_{13} bond formation, i.e., formation of the C-ring of the cephalotaxine structure.



Scheme 17

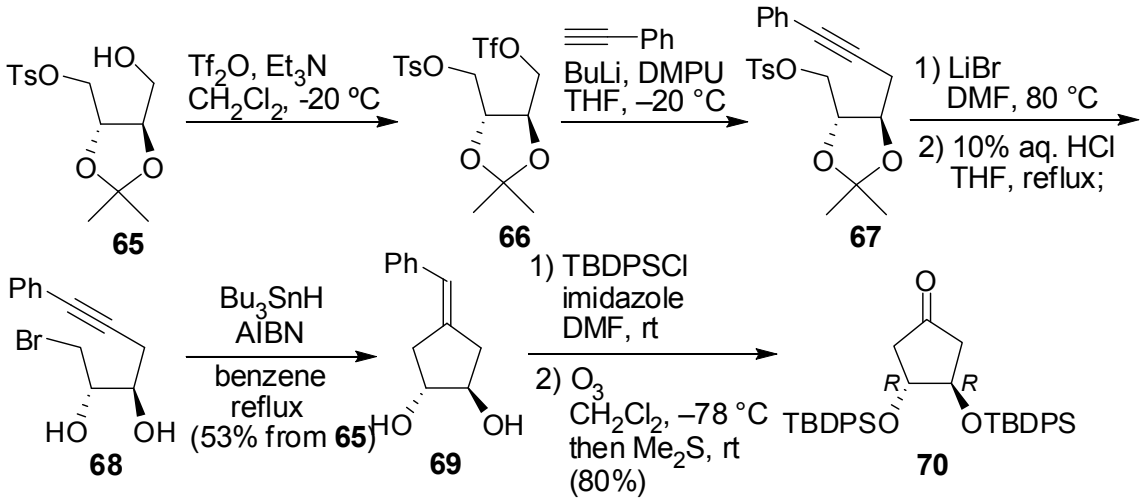
When compound **62** was treated with Bu_3SnH/ACN in boiling toluene, a cephalotaxine skeleton **64** was obtained via a α-amidoyl radical **63** (Scheme 18).[28] Although the yield of **64** was unsatisfactory, the feature of the cyclization was a simultaneous construction the C ring of the cephalotaxine skeleton followed by the D ring.

We then applied this method to the synthesis of (−)-cephalotaxine (**77**) (**60**) (Scheme 20). Scheme 19 shows the synthesis of optically active cyclopentanone **70**. Triflate **66** was prepared from diethyl D-tartrate via tosylate **6**5, and the following reaction with lithium phenylacetylide gave acetylene **67**.



Scheme 18

Bromination of **67** with lithium bromide followed by removal of acetonide afforded diol **68**. Then diol **68** underwent Bu_3SnH-mediated radical cyclization to give five-membered product **69**. Protection of **69** with TBDPSCl followed by ozonolysis afforded the desired cyclopentanone **70** (Scheme 19).



Scheme 19

We next examined the synthesis of a radical of precursor and its radical cascade (Scheme 20). Condensation of amine **71** with cyclopentanone **70** in the presence of $Ti(O\textit{i}Pr)_4$ afforded the corresponding imine, which was acylated with acryloyl chloride to give enamide **72**. On treatment with Bu_3SnH in the presence of ACN in boiling chlorobenzene, a radical cascade of enamide **72** occurred to

give desired pentacyclic compound **73**. The ^{1}H NMR spectrum of **73** showed it to be a single isomer having a stereochemistry as depicted in Scheme 20. Removal of the two TBDPS groups with TBAF gave **74**. Treatment of **74** with DMSO in the presence of TFAA afforded oxidized compound **75**. By using the known procedure, ketone **75** was treated with methoxytrimethylsilane to give methoxy ketone **76**. Compound **76** was reduced with alane to give (−)-cephalotaxine (**60**),[29] $[\alpha]_D$ −185 (*c* = 0.175, $CHCl_3$) [lit,[30] $[\alpha]_D$ −182 (*c* = 0.21, $CHCl_3$)].

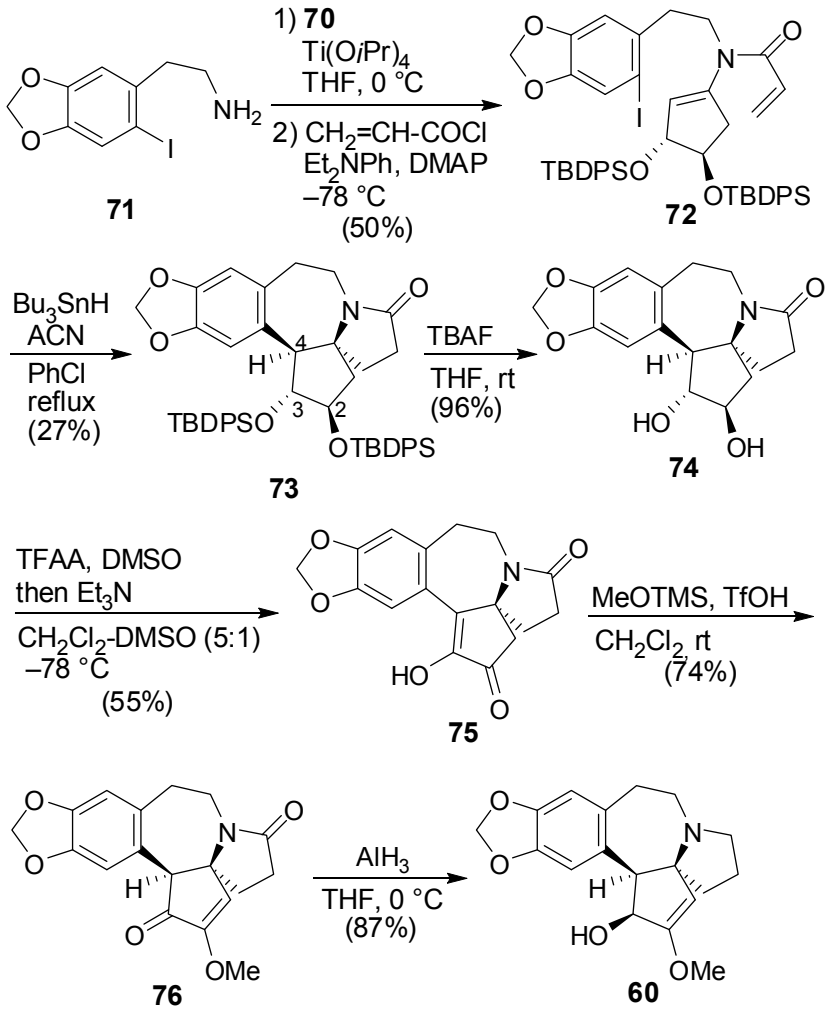
Synthesis of Stemonamide and Isostemonamide

The *Stemona* alkaloids (–)-stemonamide (**77**) and (–)-isostemonamide (**78**) and their reduced compounds, (±)-stemonamine (**79**) and (±)-isostemonamine (**80**) (Scheme 21), were isolated from the roots of *Stemona japonica*, which have been used in Chinese and Japanese folk medicines as cough medicines and insecticides. Their tetracyclic structure including contiguous spirocyclic quaternary centers provides attractive target molecules for total synthesis.

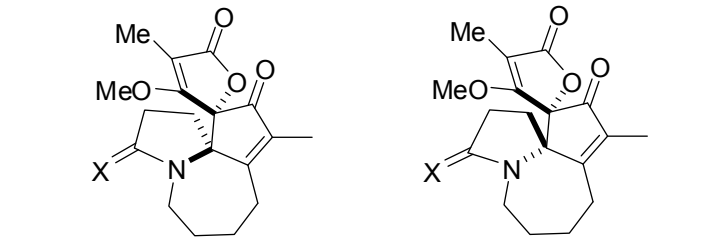
The above radical cascade involving a 7-*endo*-trig selective cyclization of an alkyl radical onto an olefinic bond of enamides could be applied to the radical cascade of an alkyl radical derived from **81** (Scheme 22). Treatment of **81** with Bu_3SnH/ACN gave a 1:1 mixture of radical cascade products **83** and **84** via the α–amidoyl radical **82** (Scheme 22).

The mixture of compounds **83** and **84** was then subjected to an aldol reaction with benzaldehyde to give an inseparable mixture of α,β-unsaturated ketones **85a,b** (Scheme 23). A subsequent addition reaction of **85a,b** with lithium ethyl propiolate afforded the adducts **86** and **87** in 50% and 48% isolated yields, respectively. X-Ray crystallographic analysis of **86** and **87** confirmed their structures, indicating that the phenyl groups of the mixture **85a,b** have stereochemistries as depicted in Scheme 23. Formation of **86** and **87** might be a result of an attack of lithium ethyl propiolate on the convex faces of **85a** and **85b**, respectively.

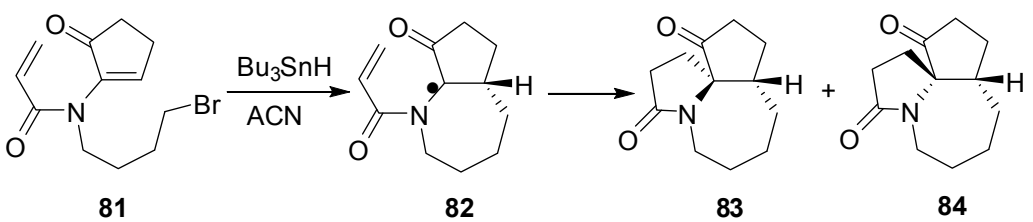
Treatment of **86** with magnesium methoxide in boiling MeOH afforded methyl tetronate (β-methoxy α,β-unsaturated lactone) **88** (Scheme 24). α-Methylation of the α,β-unsaturated bond of **88** with LDA/methyl iodide failed. Hence, an alternative method of α-methylation was examined. Iodination of **88** with *N*-iodosuccinimide (NIS) in the presence of trifluoromethanesulfonic acid (TfOH) gave iodide **89**. Treatment of compound **89** with trimethylboroxine in the presence of $PdCl_2(dppf)_2$ (Suzuki-Miyaura coupling) afforded methylated compound **90** in high yield.



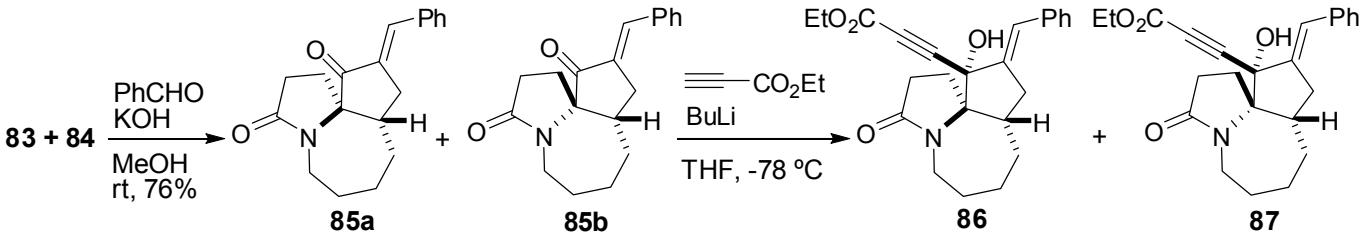
Scheme 20



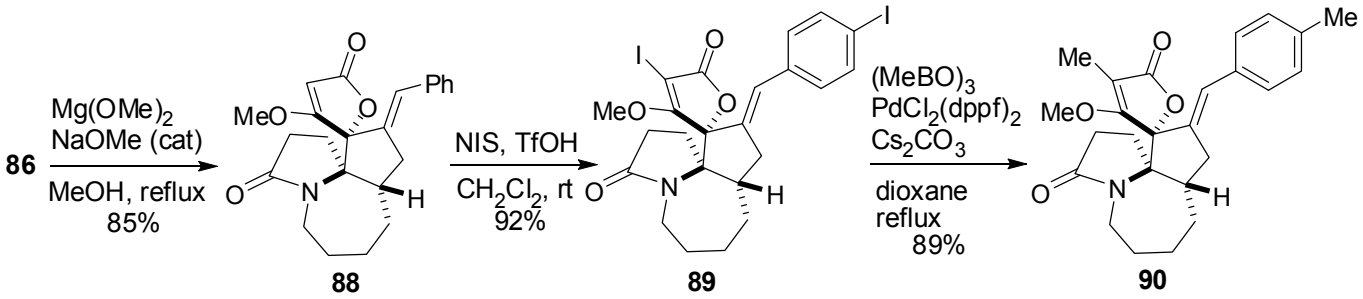
Scheme 21



Scheme 22

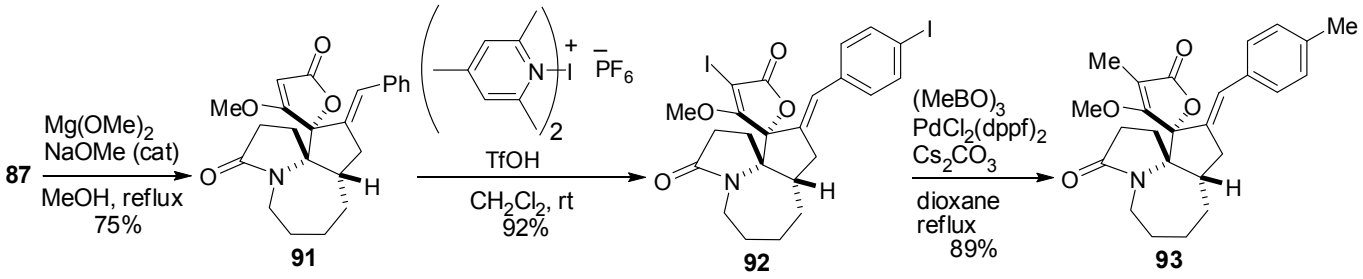


Scheme 23



Scheme 24

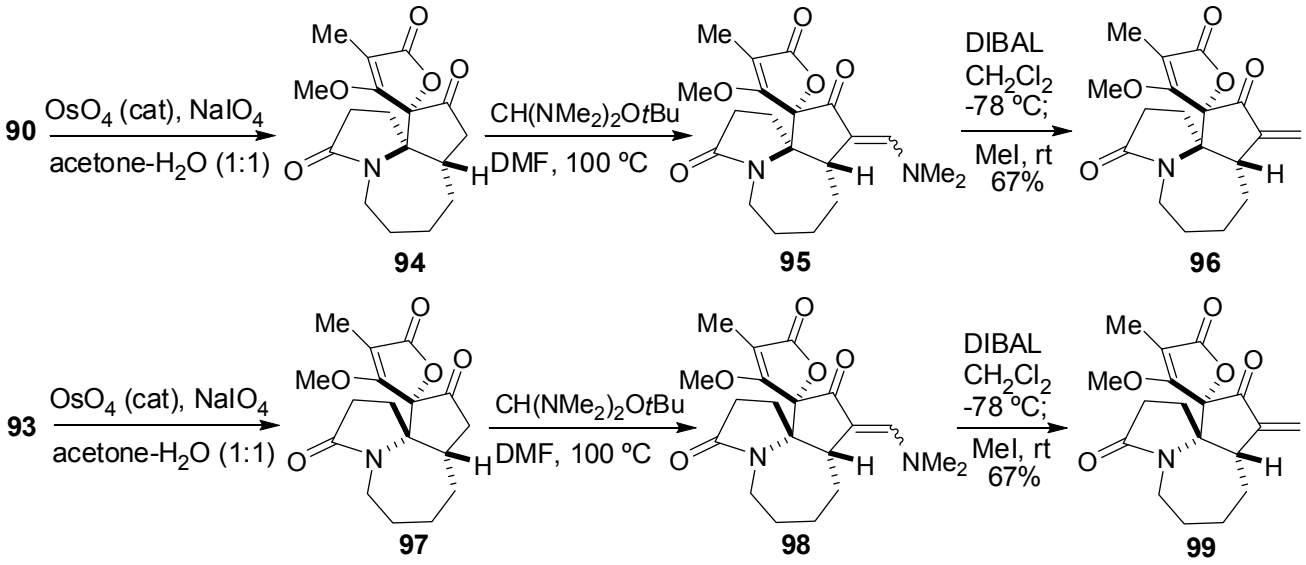
Similarly, iodination of compound **91**, prepared from **87** with magnesium methoxide, by bis(trimethylpyridine)iodonium hexafluorophosphate in the presence of TfOH gave **92** Iodination NIS/TfOH gave an unsatisfactory result. Suzuki-Miyaura coupling of **92** with trimethylboroxine afforded compound **93** (Scheme 25).



Scheme 25

Oxidative cleavage of alkene **91** with $OsO_4/NaIO_4$ gave ketone **94**. α-Methylenation of ketone **94** with Eschenmoser's salt in the presence of various bases such as KH and LDA afforded unsaturated ketone **95**, but the yield was low. Similar α-methylenation using paraformaldehyde/*N*-methylanilinium trifluoroacetate also gave an unsatisfactory result. We therefore examined another route to **96**. Treatment of ketone **94** with *tert*-butoxybis(dimethylamino)methane (Bredereck's reagent) gave

enaminone **95**, whose reduction with DIBAL followed by methylation with MeI afforded **96**. Similarly, compound **93** was converted to α -methylenated ketone **100** (Scheme 26).



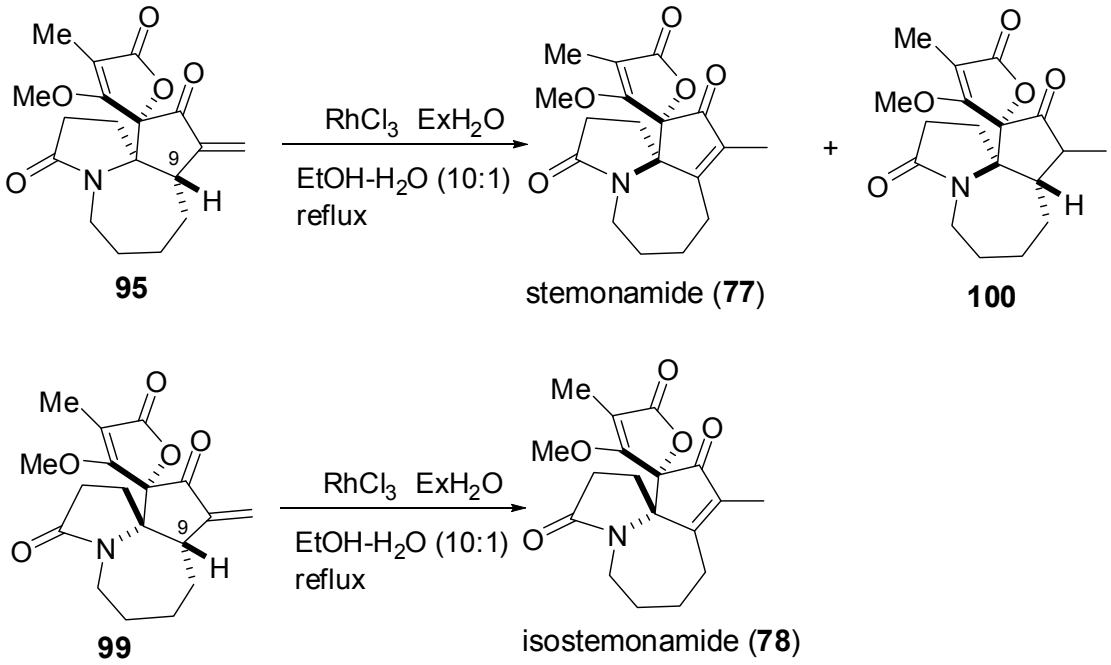
Scheme 26

Finally, $RhCl_3$-mediated isomerization of the double bond of *exo*-methylene ketone **96** gave (±)-stemonamide (**77**) (mp 232-233 °C, lit.[31] mp 240-241 °C) along with **100** in 31% and 63% yields, respectively (Scheme 27).[32] ^{1}H NMR spectra of the unexpected compound **100** showed it to be a single stereoisomer. It is presumed that an attack of $RhCl_3$ on the β-face of 9-H of **95** brings about isomerization of the double bond to give (±)-**77**, whereas when $RhCl_3$ attacks the opposite side (α-face) of 9-H, reduction of the double bond with $RhCl_3$ takes place to give **100**. Therefore, the methyl group of **100** seemed to be a β-orientation.

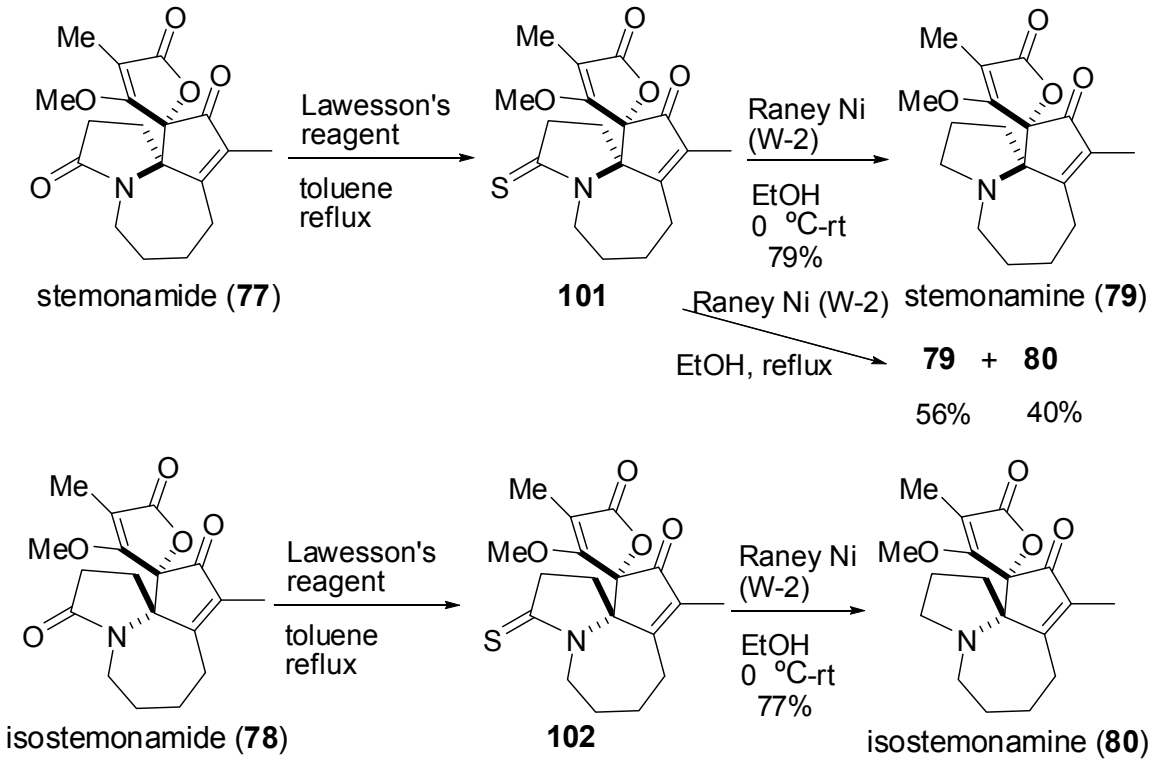
On the other hand, $RhCl_3$ attacked on the β-face of 9-H of **99** to afford (±)-isostemonamide (**78**) (mp 223-224 °C, lit.[31] mp 225-227 °C) quantitatively.[32]

Synthesis of (±)-Stemonamine and (±)-Isostemonamine

(±)-Stemonamine (**79**) and (±)-Isostemonamine (**80**) can easily be interconverted to each other and, hence (±)-stemonamine (**79**) was obtained by reduction of thioamide **101,** prepared from stemonamide (**77**), at low temperatures (0 °C to room temperature) in EtOH with Raney Ni (Scheme 28).[32b]



Scheme 27



Scheme 28

Similarly, (±)-isostemonamine (**80**) was obtained by reduction of thioamide **102**, prepared from isostemonamide (**78**).

If the reduction of thioamide **101**, prepared from stemonamide (**77**), was carried out in refluxing EtOH, a mixture of (±)-stemonamine (**79**) and (±)-isostemonamine (**80**) was obtained in 56% and 40% yields, respectively.

CONCLUSIONS

We found that carbamoylmethyl radicals generated from the corresponding α-chloro(bromo)acetamides work well as reactive species to give various alkaloids and that an exo mode of cyclization onto olefins of enamides can be shifted to an endo mode by a positional change of their carbonyl group of enamides and disclosed the new synthesis of several alkaloids including (–)-cephalotaxine using a radical cascade initiated by endo-selective cyclization. Further studies directed toward the synthesis of other alkaloids using this strategy are now in progress in our laboratory.

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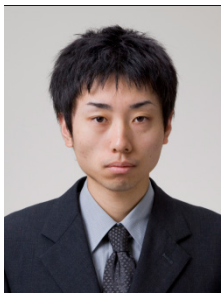

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