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## SYNTHETIC STUDIES ON NITROGEN-CONTAINING FUSED-HETEROCYCLIC COMPOUNDS BASED ON THERMAL ELECTROCYCLIC REACTIONS OF $6\pi$ -ELECTRON AND AZA $6\pi$ -ELECTRON SYSTEMS

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**Abstract** – Syntheses of carbazole alkaloids and indoles by an allene-mediated electrocyclic reaction of a  $6\pi$ -electron system (II) through a tautomeric process, and syntheses of several fused pyridine ring systems including alkaloids by a thermal electrocyclic reaction of an aza  $6\pi$ -electron system having an oxime or isocyanate (III) through either the elimination of a small molecule or a tautomeric process are described.

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### I. INTRODUCTION

We are currently interested in the synthesis of the nitrogen-containing condensed heteroaromatic compounds by a thermal electrocyclic reaction of either a  $6\pi$ -electron or an aza  $6\pi$ -electron system. A thermal electrocyclic reaction of a  $6\pi$ -electron system to cyclohexadiene occurs as a disrotatory reversible process.<sup>1</sup> The irreversible conversion of cyclohexadiene can be controlled by the elimination of a small molecule. The replacement of one carbon atom of a  $6\pi$ -electron system with a nitrogen atom produces an aza  $6\pi$ -electron system. The thermal electrocyclic reaction of an aza  $6\pi$ -electron system to

dihydropyridine occurs in a similar process. The irreversible conversion of dihydropyridine should be controlled by the elimination of a small molecule. In addition, a thermal electrocyclic reaction of a  $6\pi$ -electron or an aza  $6\pi$ -electron system where one member of the double bond is a part of an aromatic or heteroaromatic ring should provide a variety of fused heteroaromatic compounds. Since 1980, new syntheses of carbazole alkaloids including pyrido[4.5-*b*]carbazole alkaloids based on a thermal electrocyclic reaction of a  $6\pi$ -electron system involving the indole 2,3-bond have been reported.<sup>2a-f,3a,b,d,e</sup> Moreover, syntheses of thieno[3,2-*c*]pyridine and pyrido[4,3-*b*]indole ( $\gamma$ -carboline) using the thermal electrocyclic reaction of aza  $6\pi$ -electron systems involving the thiophene 2,3-bond and the indole 2,3-bond were initially reported in 1984,<sup>2g,3a</sup> and subsequently the methodology involving the indole 2,3-bond was proved to be an efficient procedure for nitramarine ( $\beta$ -carboline),<sup>2h,3a</sup> Trp-P-1 and Trp-P-2 ( $\gamma$ -carbolines),<sup>2ij,3a</sup> and A $\alpha$ C and MeA $\alpha$ C ( $\alpha$ -carbolines).<sup>2k,3a</sup> These results have been reviewed as [*b*]-annelated indoles by thermal electrocyclic reactions, except for thieno[3,2-*c*]pyridine, from 1980 until 1995.<sup>3a</sup> Furthermore, the methodology involving the benzene 1,2-bond was initiated to prepare isoquinoline<sup>2l</sup> and the isoquinoline part of aaptamine.<sup>2m,n</sup> To develop milder conditions of a thermal electrocyclic reaction for the  $6\pi$ -electron system, construction of a highly-substituted carbazole framework was established using an allene-mediated electrocyclic reaction followed by a tautomeric process involving the indole 2,3-bond. Taking advantage of this strategy, several total syntheses of carbazole alkaloids were achieved (II).<sup>3c-e</sup> Furthermore, applications of the thermal electrocyclic reaction of aza  $6\pi$ -electron systems involving the imidazole 4,5-bond, the indole 2,3-bond, and the benzene 1,2-bond have been also developed through either the oximes or the isocyanate (III).<sup>3c</sup> These results from 1993 through 2010 are described in the present review.

## II. SYNTHETIC STUDIES USING AN ALLENE-MEDIATED ELECTROCYCLIC REACTION

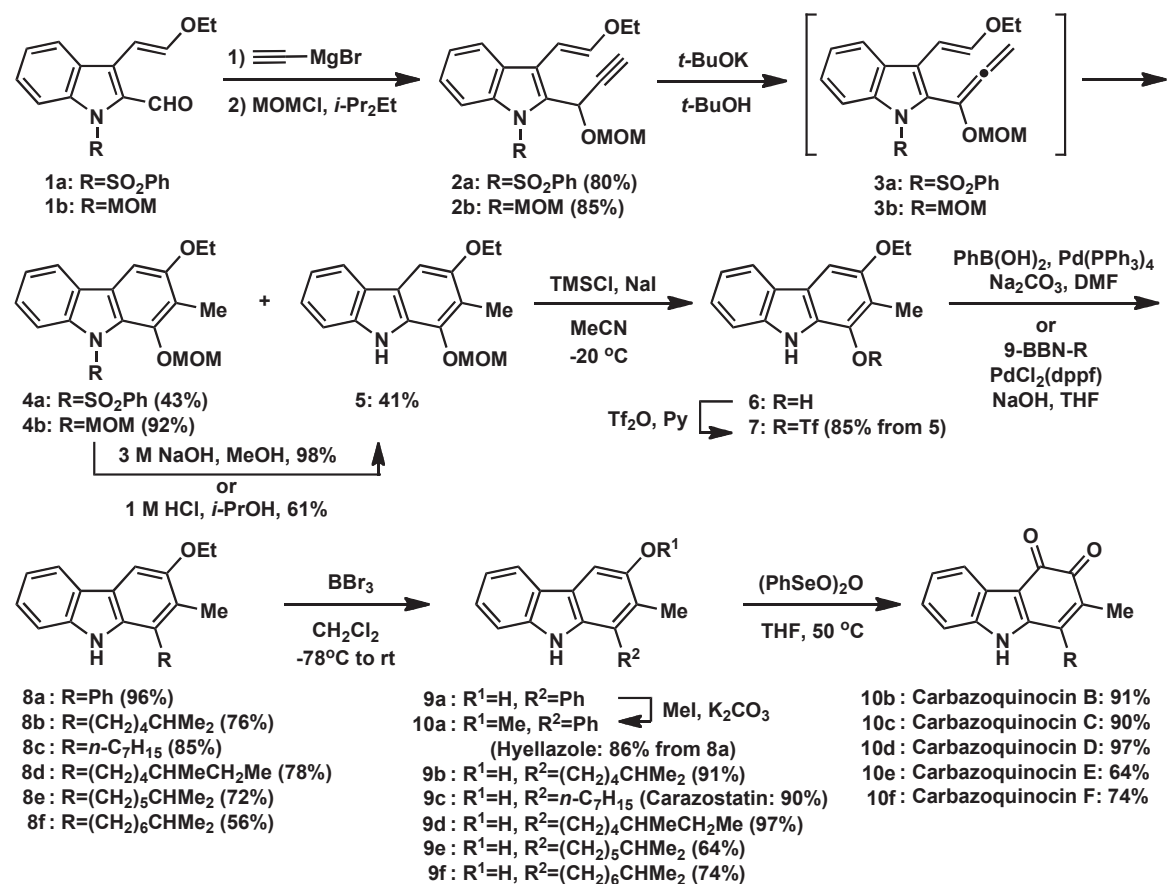
### II-1. Synthesis of carbazoles and carbazole alkaloids through 2-allenylindoles

#### II-1-1. Synthesis of carazostatin, hyellazole, and carbazoquinocins

Total syntheses of carazostatin (**9c**) isolated from *Streptomyces chromofuscus*,<sup>4</sup> hyellazole (**10a**) isolated from blue-green alga *Hyella caespitosa*,<sup>5</sup> and carbazoquinocins B-F (**10b-f**) isolated from *Streptomyces violaceus* 2448-SVT<sup>6</sup> have been achieved (Scheme 1). Treatment of the alkenylindole **1a** with ethynylmagnesium bromide, followed by etherification of the resulting alcohol with chloromethyl methyl ether (MOMCl), yielded the 3-alkenyl-2-propargylindole **2a**. In a similar manner, compound **2b** was obtained from **1b** in two steps. Compound **2a** was heated at 90 °C in *t*-BuOH in the presence of *t*-BuOK, according to the procedure of Kanematsu for allene generation,<sup>7</sup> to yield the expected carbazole **4a** together with the *N*-deprotected carbazole **5**. By contrast, heating the *N*-MOM-3-alkenyl-2-propargylindole **2b** in *t*-BuOH in the presence of *t*-BuOK produced the

*N*-MOM-carbazole **4b**. The *N*-protecting groups of **4a** and **4b** were removed, respectively, to form the same carbazole **5**. Treatment of **5** with TMSCl and NaI followed by treatment of trifluoromethanesulfonic anhydride (Tf<sub>2</sub>O) and pyridine gave the triflate **7**. The Suzuki-Miyaura reaction<sup>8</sup> between **7** and phenylboronic acid gave the 1-phenylcarbazole **8a**, which was treated with BBr<sub>3</sub> followed by *O*-methylation to produce hyellazole (**10a**). The cross-coupling reaction between **7** and 9-heptyl-9-BBN also gave the 1-heptylcarbazole **8c**, which was treated with BBr<sub>3</sub> to produce carazostatin (**9c**). Carbazocinocin C (**10c**) was readily obtained from carazostatin (**9c**) through an oxidation step with (PhSeO)<sub>2</sub>O. In a similar way, triflate **7** was subjected to a Pd-catalyzed cross-coupling reaction with 9-alkyl-9-BBN to give the 1-alkylcarbazoles **8b** and **8d-f**. Subsequent treatment of **8d** and **8d-f** with BBr<sub>3</sub> afforded 3-hydroxycarbazoles **9b** and **9d-f**, which were oxidized with (PhSeO)<sub>2</sub>O to yield the corresponding carbazoquinocins B (**10b**), D (**10d**), E (**10e**), and F (**10f**), respectively.<sup>9</sup>

Scheme 1

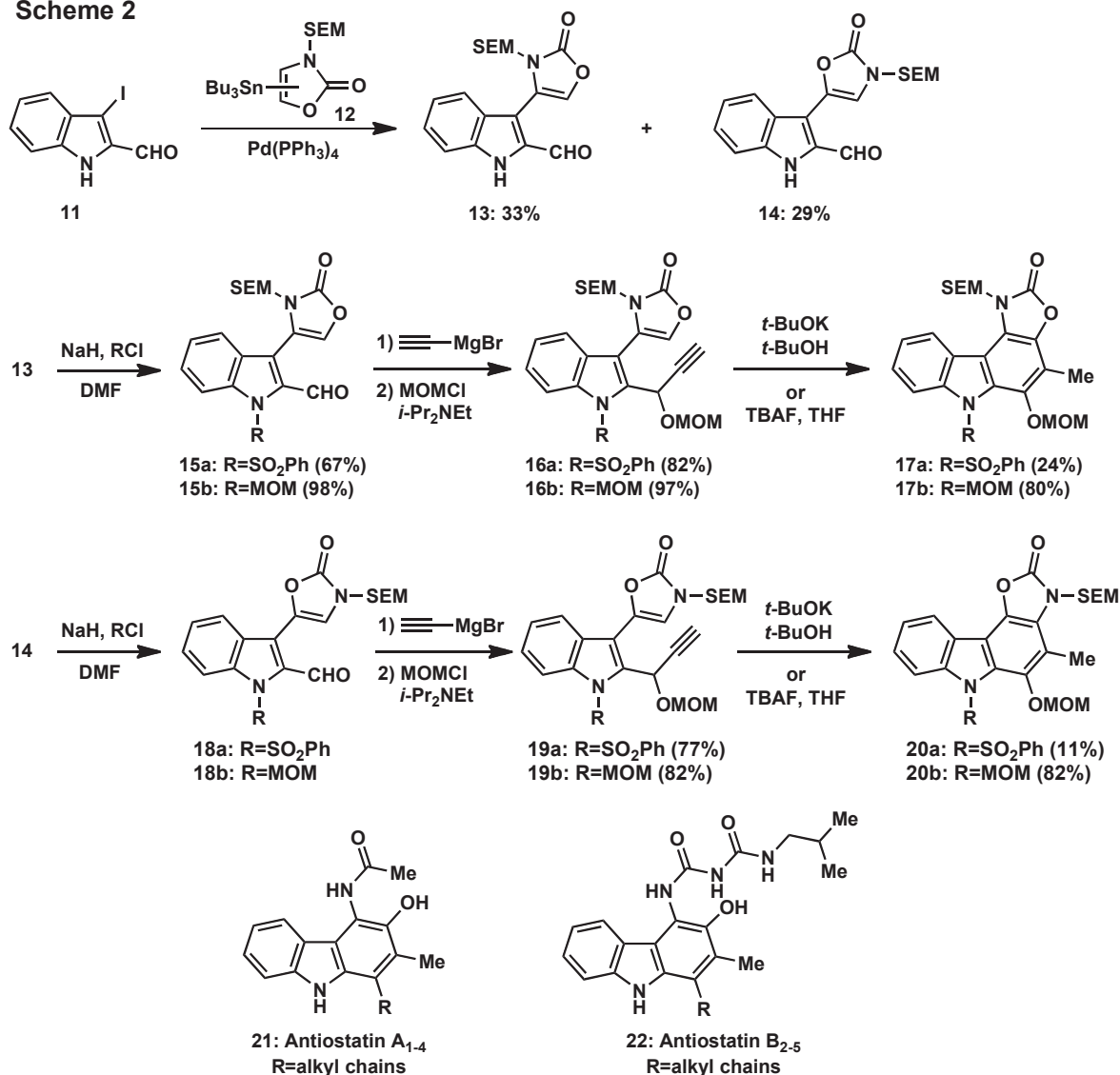


## II-1-2. Synthesis of oxazolo[5,4-*c*]carbazole and oxazolo[4,5-*c*]carbazole

To synthesize the highly substituted carbazole alkaloids, antiostatins A<sub>1-4</sub> (**21**) and antiostatins B<sub>2-5</sub> (**22**),<sup>10</sup> we assumed that a new type of tetracyclic oxazolo[5,4-*c*]carbazole **17** would be a functionalized key-intermediate (Scheme 2). Treatment of the *N*-SEM-oxazolone with *t*-BuLi followed by tributyltin chloride gave the stannyloxazolone **12**, which was subjected to a Pd-catalyzed cross-coupling reaction<sup>11</sup>

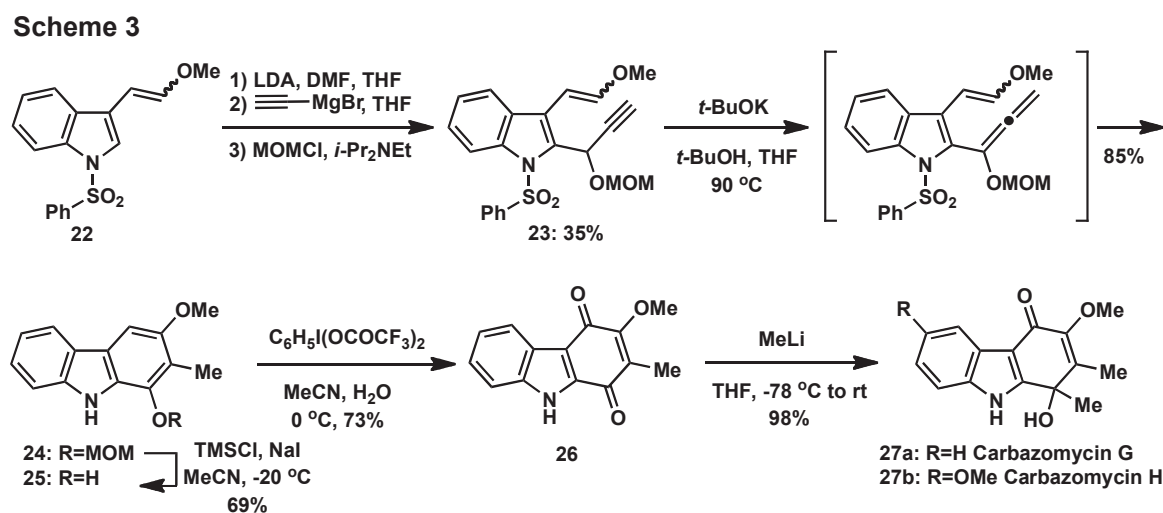
with 3-iodoindole **11** to give an approximately 1:1 mixture of two isomeric 3-oxazolyloindoles **13** and **14**. The directed metalation of SEM-oxazolone **12** with *t*-BuLi did not work regioselectively. Subsequent treatment of indole **13** with NaH followed by the addition of benzenesulfonyl chloride or MOMCl gave **15a** and **15b**, respectively. The Grignard reaction of 2-formylindole **15a** and **15b** with ethynylmagnesium bromide yielded the propargyl alcohols, which were protected with MOMCl to give MOM-ethers **16a** and **16b**. Then, **16a** was heated in *t*-BuOH/THF (3:1) in the presence of *t*-BuOK at 90 °C for 3 h to give the tetracyclic carbazole **17a**. The *N*-MOM-indole **16b** was heated in THF in the presence of tetrabutylammonium fluoride (TBAF) at 90 °C for 0.5 h to produce the tetracyclic carbazole **17b**. A base exchange was not effective in either reaction. On the other hand, tetracyclic carbazoles **20a** and **20b** were prepared from the tentative product **14** in a similar manner. The structures of two tetracyclic *N*-benzenesulfonylcarbazoles **17a** and **20a** were determined by 2D-NOESY NMR spectra.<sup>12</sup>

Scheme 2



### II-1-3. Synthesis of an antibiotic carbazole alkaloid, carbazomycin G

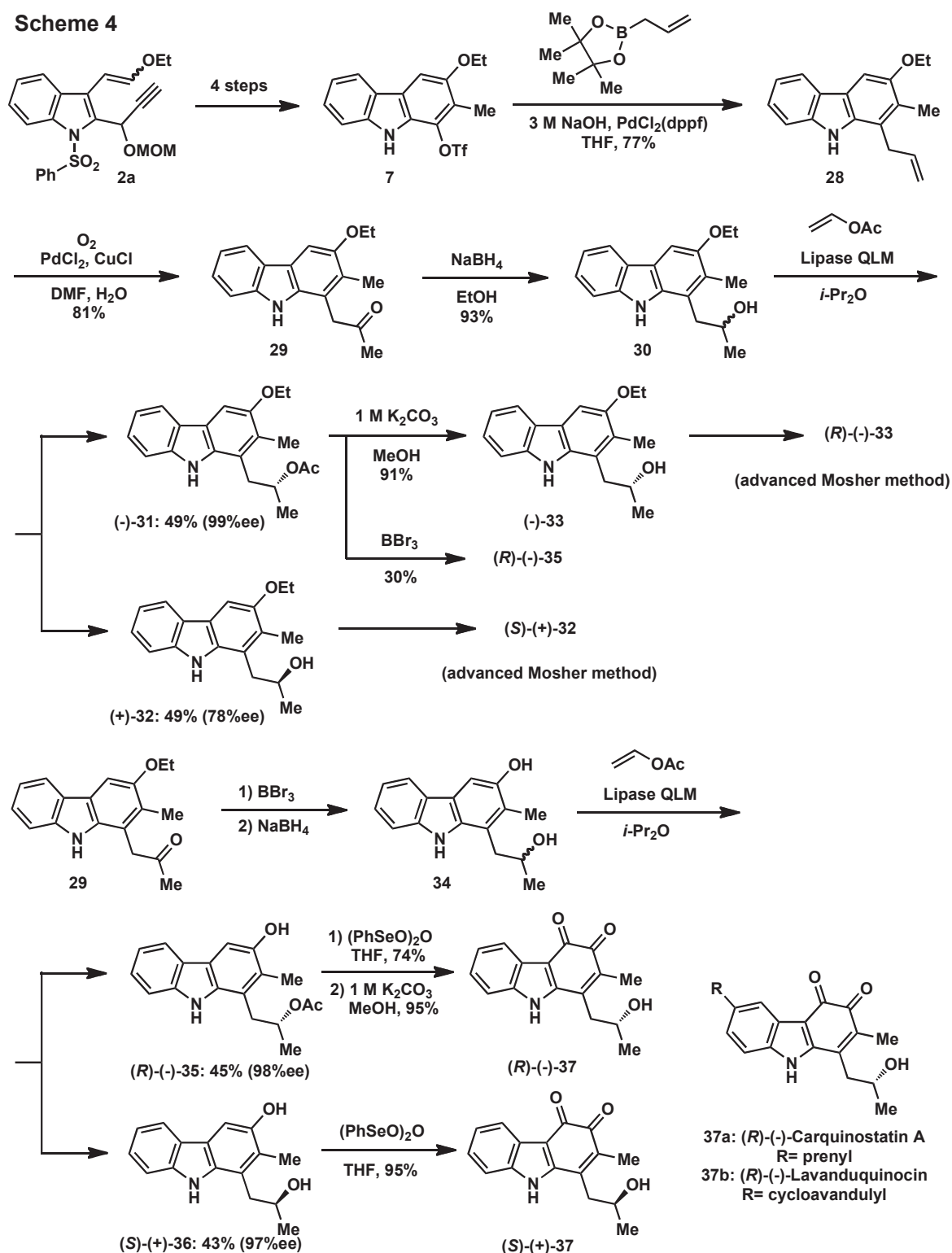
Carbazomycins G (**27a**) and H (**27b**) were isolated from *Streptoverticillium ehimense* as a racemate together with carbazomycins A-F.<sup>13</sup> The total synthesis of carbazomycin G (**27a**) was completed in seven steps (Scheme 3). The required 3-alkenyl-2-propargylindole **23** was prepared from the *N*-benzenesulfonyl-3-(2-methoxyethenyl)indole (**22**) in three steps through the indole-3-carbaldehyde. The precursor **23** was subjected to an allene-mediated electrocyclic reaction using *t*-BuOK in *t*-BuOH and THF at 90 °C to produce the desired 1,3-dioxygenated carbazole **24**. Cleavage of the MOM-ether of **24** with TMSCl and NaI gave the 1-hydroxycarbazole **25**. The oxidation to carbazole-1,4-quinone **26** from the phenol proceeded by [bis(trifluoroacetoxy)iodo]benzene in aqueous CH<sub>3</sub>CN. Other oxidizing agents did not work well in this case. Finally, the nucleophilic addition of the carbazole-1,4-quinone **26** with MeLi provided carbazomycin G (**27a**).<sup>14</sup>



### II-1-4. Synthesis of desprenyl-carquinostatin A and descycloavandulyl-lavanduquinocin

Carbazole-3,4-quinone alkaloids, carquinostatin A (**37a**) and lavanduquinocin (**37b**) were isolated from *Streptomyces exfoliates* 2419-SVT2<sup>15a</sup> and *Streptomyces viridochromogenes*,<sup>15b</sup> respectively. An asymmetric synthesis of the common carbazole framework, 6-desprenyl-carquinostatin A **37** and descycloavandulyl-lavanduquinocin **37**, toward the total synthesis of carquinostatin A (**37a**) and lavanduquinocin (**37b**) was established (Scheme 4). The required carbazole 1-triflate **7** was prepared from 3-alkenyl-2-propargylindole **2a** in four steps (see: II-1-1). The 1-allylcarbazole **28** was synthesized by the Suzuki-Miyaura reaction<sup>8</sup> between the triflate **7** and allylboronic acid pinacol ester. Subsequently, the Wacker reaction of **28** gave the acetonilcarbazole **29** followed by reduction of **29** with NaBH<sub>4</sub> provided the racemic alcohol **30**. Lipase QLM catalysis of the enantioselective acetylation of the racemic alcohol **30** gave the (-)-acetate **31** and the (+)-acetate **32** with high enantioselectivity. The absolute

Scheme 4



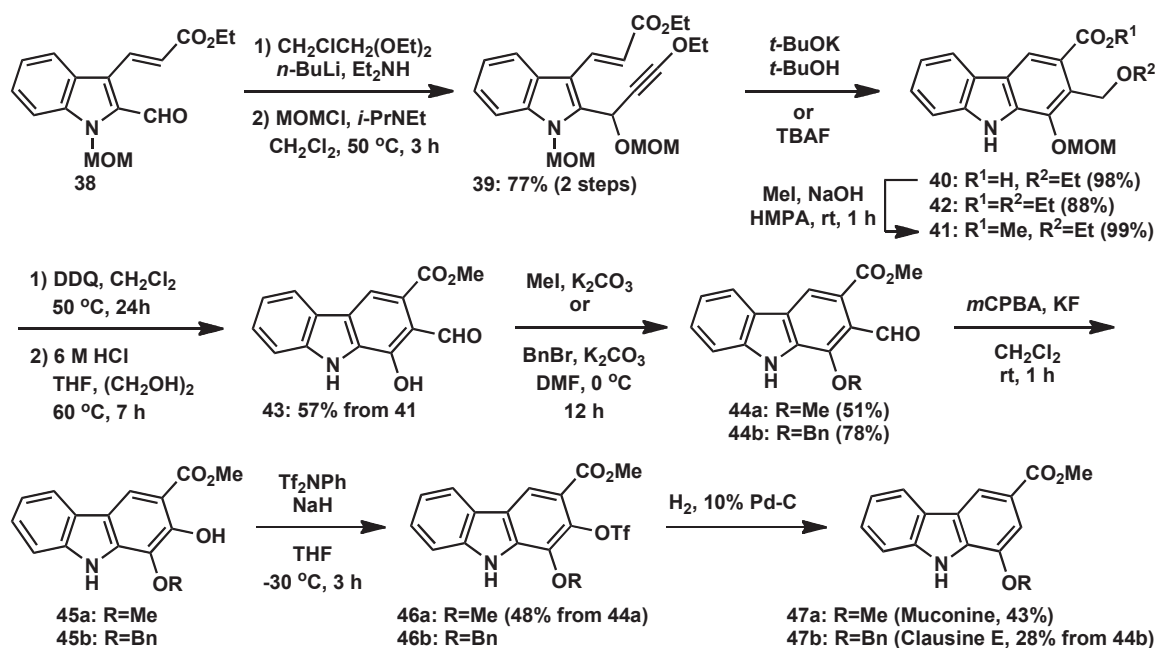
stereochemistries of the (-)-alcohol **33** and the (+)-alcohol **32** were determined to be *R*- and *S*-configurations, respectively, by the advanced Mosher method. Cleavage of the ethyl ether of **29** with  $BBr_3$  afforded the 3-hydroxycarbazole **34**, which was reduced with  $NaBH_4$  to provide the racemic alcohol **34**. Subsequent lipase QLM catalyzed enantioselective esterification of **34** in the same manner gave the (-)-acetate **35** and the (+)-alcohol **36**, respectively. This (-)-acetate **35** was the same as the (*R*)-(-)-acetate **35** derived from (-)-**31** by treatment with  $BBr_3$ . Oxidation of the (*R*)-(-)-acetate **35** followed by hydrolysis

afforded the (*R*)-(-)-6-desprenyl-carquinostatin [and the (*R*)-(-)-descycloavandulyl-lavanduquinocin] **37**. In addition, oxidation of the (*S*)-(+)-alcohol **36** provided the (*S*)-(+)-**37** as an enantiomer.<sup>16</sup>

## II-1-5. Synthesis of 1,3-disubstituted carbazole alkaloids, mukonine and clausine E

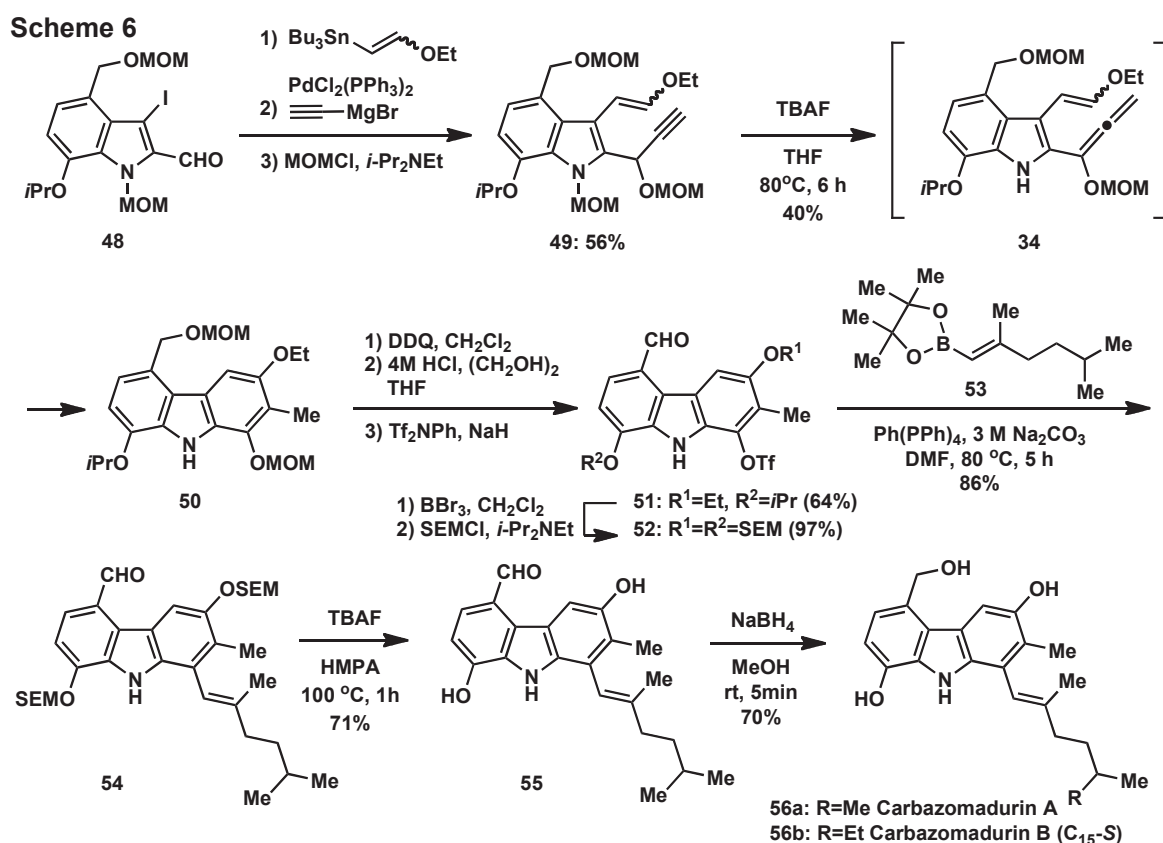
The simple 1-oxygenated 3-substituted carbazole alkaloids mukonine (**47a**) and clausine E (**47b**) (clauzoline I) were isolated from *Murraya koenigii* and *Clausena excavata* (and *anisata*), together with the related alkaloids.<sup>17</sup> Two alkaloids were newly synthesized (Scheme 5). Nucleophilic addition reaction of ethyl 3-[2-formyl-*N*-(methoxymethyl)indol-3-yl]acrylate **38** with ethoxyacetylide (prepared from chloroacetaldehyde diethyl acetal with *n*-BuLi and diethylamine) gave the propargyl alcohol, which was treated with MOMCl to produce the propargyl ether **39**. An allene-mediated electrocyclic reaction of **39** was carried out by *t*-BuOK to yield the exclusively carbazole-3-carboxylic acid **40** through a ring closure together with hydrolysis. On the other hand, the same reaction of **39** using TBAF gave the ester **42**. The carbazole-3-carboxylic acid **40** was converted to the methyl carbazole-3-carboxylate **41**. Subsequent oxidation of the alkoxyethyl group at the 2-position of **42** with DDQ provided the 2-formyl-1-hydroxycarbazole **43**. Alkylation of the 1-hydroxycarbazole **43** was carried out by MeI or benzyl bromide to give the 1-methoxycarbazole **44a** or 1-benzyloxycarbazole **44b**, respectively. The Baeyer-Villiger reaction of **44a** and **44b** with *m*-chloroperbenzoic acid (*m*CPBA) afforded 2-hydroxycarbazole **45a** and **45b**, respectively. Additional treatment of **45a** and **45b** with *N*-phenyl(bistrifluoromethanesulfonyl)amide (Tf<sub>2</sub>NPh) and NaH gave the triflates **46a** and **46b**, which were subjected to hydrogenolysis to produce mukonine (**47a**) and clausine E (**47b**) along with *O*-debenzylation.<sup>18</sup>

Scheme 5



## II-1-6. Synthesis of the poly-substituted carbazole alkaloid carbazomadurin A

Carbazomadurins A (**56a**) and B (**56b**) were isolated from *Actinomadura madurae* 2808-SV1.<sup>19</sup> The required 7-oxygenated 2,3,4,7-tetrasubstituted indole **48** was prepared from the known ethyl 7-isopropoxyindole-2-carboxylate in six steps (57%). We then synthesized 1,3,8-trioxygenated 1,2,3,5,8-pentasubstituted carbazole **50** from **48**. The Pd-catalyzed cross-coupling reaction<sup>11</sup> of 3-iodoindole **48** with tributyl(2-ethoxyvinyl)tin, the Grignard reaction of the 3-alkenylindole with ethynylmagnesium bromide, followed by protection of the resulting alcohol with MOMCl gave the 3-alkenyl-2-propargylindole **49** in three steps. When **49** was heated at 90 °C in the presence of *t*-BuOK in *t*-BuOH, the expected carbazole **50** was not detected. Alternatively, treatment of **49** with TBAF in THF at 80 °C afforded the expected carbazole **50** in somewhat low yield. Oxidation of the *O*-MOM-methyl group at the C-5 position of **50** with DDQ to the 5-formylcarbazole, cleavage of the *O*-MOM group with 4M HCl to the 1-hydroxycarbazole, followed by sequential treatment of the 1-hydroxy group with Tf<sub>2</sub>NPh gave the corresponding triflate **51** in three steps. Additional cleavage of both ethers at the 3- and 8-positions of **51** with BBr<sub>3</sub> afforded the 3,8-dihydroxycarbazole, which was immediately protected with SEMCl and *i*-Pr<sub>2</sub>NEt to produce the 3,8-bis-*O*-SEM-carbazole **52**. On the other hand, a pinacol borate **53** to introduce an alkenyl side chain with an *E*-configuration at the C1 position of **52** was prepared from 5-methyl-1-hexyne. Namely, zirconium-catalyzed carboalumination of 5-methyl-1-hexyne with Me<sub>3</sub>Al and zirconocene dichloride,<sup>20</sup> followed by the addition of I<sub>2</sub> afforded *E*-alkenyl iodide. Subsequently, the





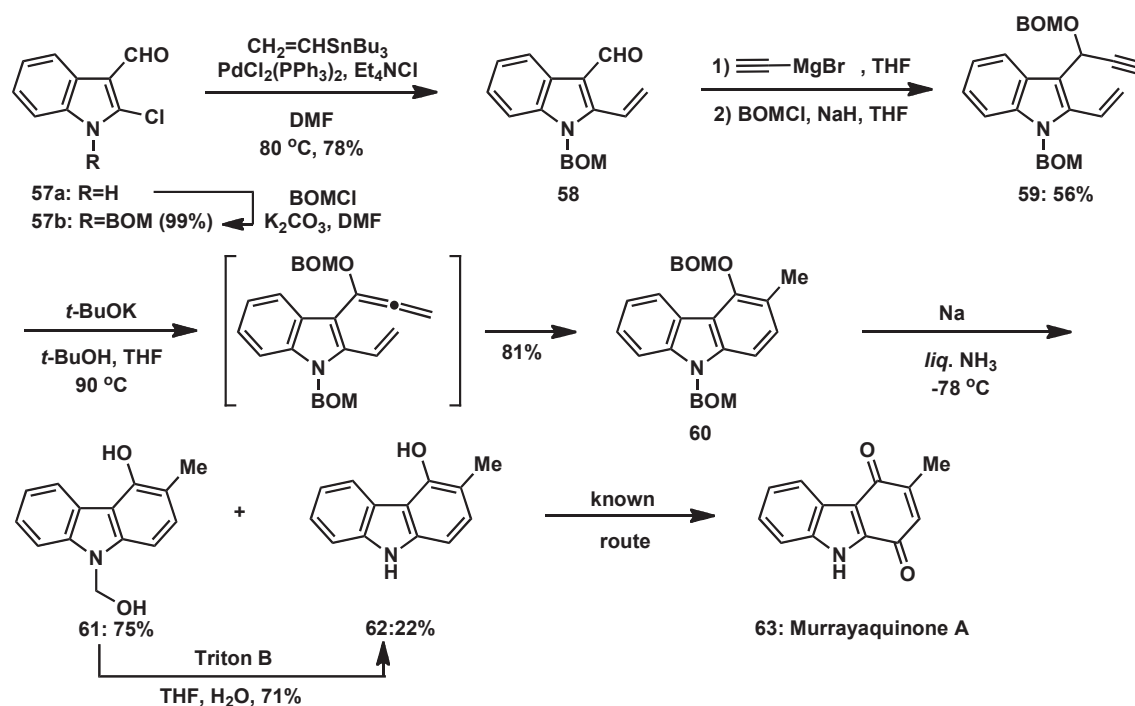
Suzuki-Miyaura reaction<sup>8</sup> of *E*-alkenyl iodide with bis(pinacolato)diboron in the presence of PdCl<sub>2</sub>(dppf) afforded the pinacol borate **53** (48% in three steps). The Suzuki-Miyaura reaction<sup>8</sup> between the triflate **52** and the pinacol borate **53** gave the 1-alkenylcarbazole **54** in good yield. Removal of both SEM groups of **54** with TBAF afforded the dihydroxycarbazole **55**. Finally, reduction of **55** with NaBH<sub>4</sub> provided carbazomadurin A (**56a**) (Scheme 6).<sup>21</sup>

## II-2. Synthesis of carbazole through a 3-allenylindole

### II-2-1. Synthesis of a carbazole-1,4-quinone alkaloid, murrayaquinone A

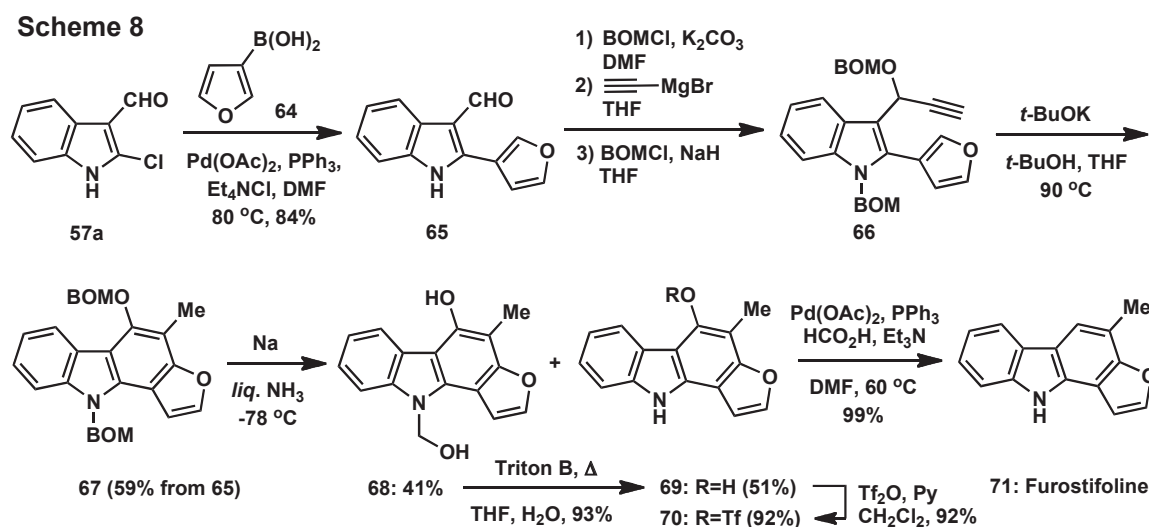
The carbazole-1,4-quinone, murrayaquinone A (**63**) was isolated from *Murraya eucrestifolia* Hayata, together with three closely related alkaloids.<sup>22</sup> For synthesis of the known 4-hydroxy-3-methylcarbazole (**62**), the benzyloxymethyl (BOM) group was used as a *N*-protecting group of 2-chloroindole-3-carbaldehyde (**57a**). Treatment of **57a** with benzyl chloromethyl ether (BOMCl) afforded the *N*-BOM-indole **57b**. The Pd-catalyzed cross-coupling reaction<sup>11</sup> between **57b** and ethenyl tributylstannane gave the 2-ethenylindole **58**. The Grignard reaction of **58** with ethynylmagnesium bromide followed by treatment of the resulting alcohol with BOMCl produced the 2-ethenyl-3-propargylindole **59**. The propargylindole **59** was subjected to a thermal electrocyclic reaction in the presence of *t*-BuOK to yield the carbazole **60**. Deprotection of the *N,O*-bis-BOM groups of **60** was carried out under the Birch condition to give a separable mixture of *N*-hydroxymethyl-4-hydroxy-3-methylcarbazole (**61**) and 4-hydroxy-3-methylcarbazole (**62**). The *N*-hydroxymethyl group of **61** was removed by heating with Triton B to yield **62**. A formal total synthesis of murrayaquinone A (**63**) was achieved (Scheme 7).<sup>23</sup>

Scheme 7



### II-2-2. Synthesis of the furo[3,2-*a*]carbazole alkaloid furostifoline

The tetracyclic furo[3,2-*a*]carbazole alkaloid furostifoline (**71**) was isolated from *Murraya eucrestifolia* Hayata along with the furo[3,2-*g*]carbazole alkaloid eustifoline D.<sup>24</sup> The cross-coupling reaction<sup>8</sup> of 2-chloroindole **57a** with furane-3-boronic acid (**64**) was carried out in the presence of Pd(OAc)<sub>2</sub> and PPh<sub>3</sub> to give the 2-(3-furyl)indole **65**. After protection of the indole nitrogen atom of **65** with BOMCl, a subsequent Grignard reaction with ethynylmagnesium bromide followed by additional protection of the resulting alcohol with BOMCl and NaH yielded the 2-(3-furyl)-3-propargylindole **66**. Compound **66** was subjected to a thermal electrocyclic reaction in the presence of *t*-BuOK to produce the 4-oxygenated furocarbazole **67**. The Birch reduction of **67** for the deprotection of *N,O*-bis-BOM groups gave a separable mixture of the expected 4-hydroxy-3-methylfuro[3,2-*a*]carbazole (**69**) and its *N*-hydroxymethylfuro[3,2-*a*]carbazole **68**. Compound **68** was converted to **69** by heating with Triton B. Finally, treatment of the phenol **69** with Tf<sub>2</sub>O and pyridine afforded the triflate **70**, which was subjected to a reductive cleavage of the 4-trifluoromethanesulfonyloxy group of **70** with Pd(OAc)<sub>2</sub> and PPh<sub>3</sub> in the presence of HCO<sub>2</sub>H and Et<sub>3</sub>N at 60 °C to give furostifoline (**71**) in excellent yield (Scheme 8).<sup>23b</sup>

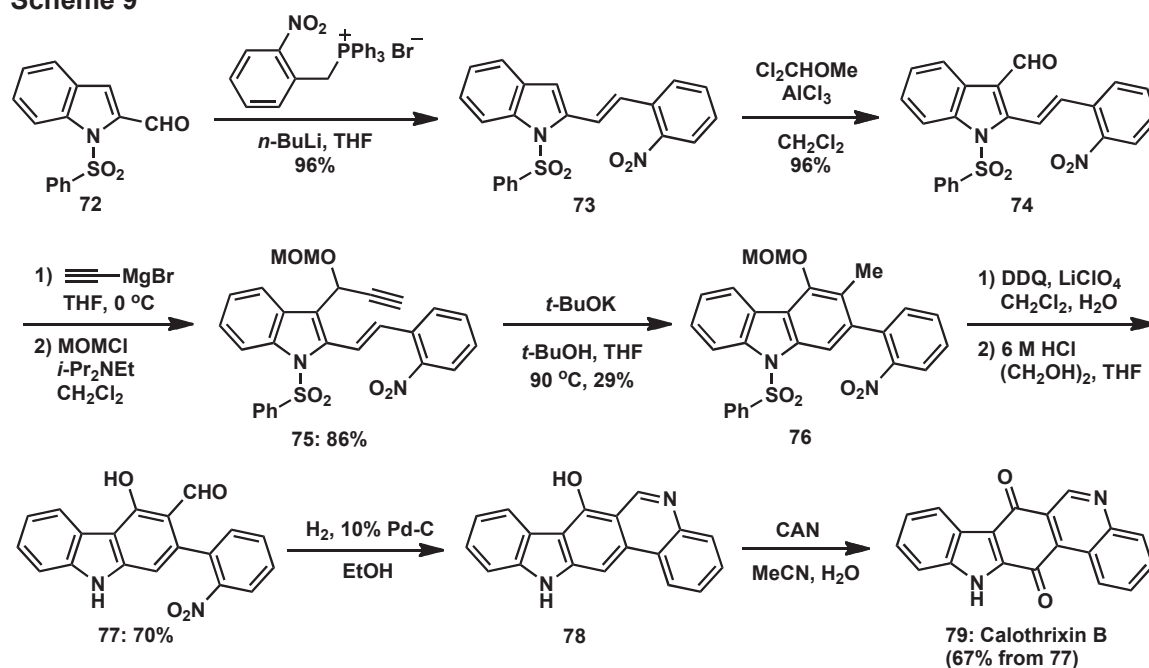


### II-2-3. Synthesis of the indolo[3,2-*j*]phenanthridine alkaloid calothrixin B

Novel indolo[3,2-*j*]phenanthridine alkaloids, calothrixins A (*N*-oxide of **79**) and B (**79**) were isolated from *Calothrix* cyanobacteria.<sup>25</sup> The Wittig reaction of indole-2-carbaldehyde **72** with 2-nitrobenzyltriphenylphosphorane gave the *trans*-2-(2-styryl)indole **73**. Subsequent treatment of **73** with Cl<sub>2</sub>CHOMe in the presence of AlCl<sub>3</sub> afforded the 2-alkenyl-3-formylindole **74**. The Grignard reaction of **74** with ethynylmagnesium bromide yielded the propargyl alcohol, which was protected with MOMCl and *i*-Pr<sub>2</sub>NEt to produce the *O*-MOM ether **75**. The 2-alkenyl-3-propargylindole **75** was subjected to a thermal electrocyclic reaction to yield the expected 4-oxygenated 2,3,4-trisubstituted carbazole **76** along

with elimination of the benzenesulfonyl group. Sequential oxidation of **76** with DDQ followed by deprotection with 6 M HCl gave the 3-formylcarbazole **77**. Reduction of the nitro group of **77** with 10% Pd-C and H<sub>2</sub> followed by condensation afforded the indolo[3,2-*j*]phenanthridine **78**, which was oxidized with cerium ammonium nitrate (CAN) to provide calothrixin B (**79**) (Scheme 9).<sup>26a,c,d</sup>

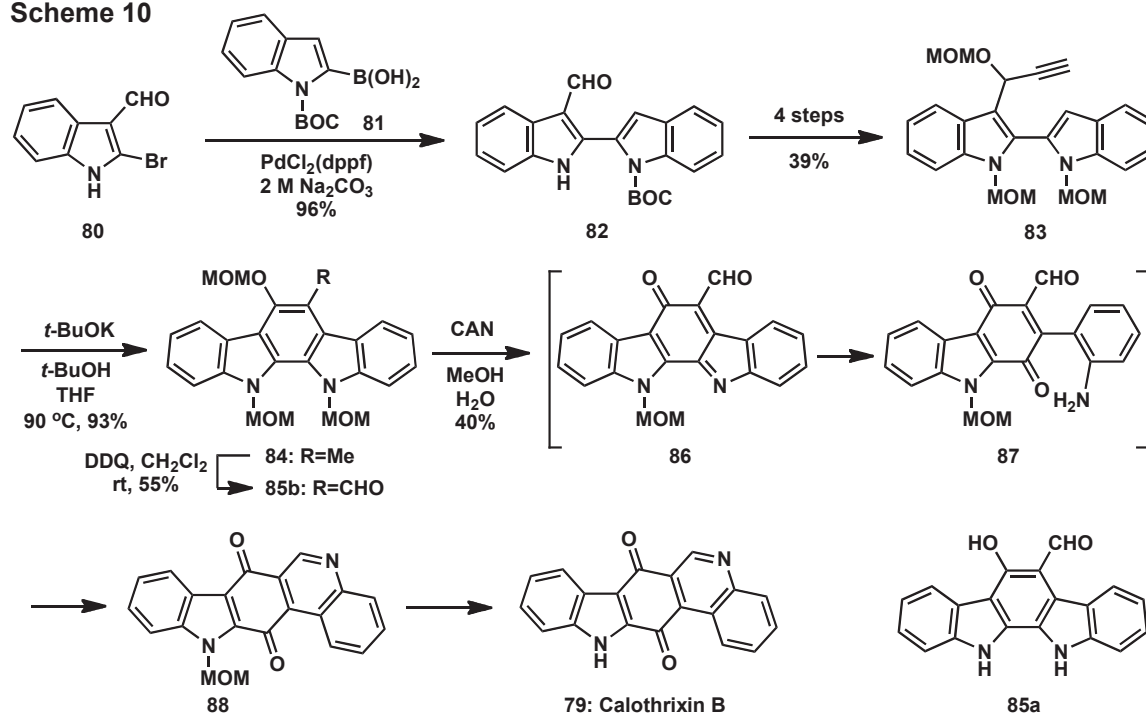
Scheme 9



## II-2-4. Biomimetic synthesis of calothrixin B

The Rickards group proposed that calothrixins A (**79**: *N*-oxide) and B (**79**) are derived from a hypothetical metabolite indolo[2,3-*a*]carbazole **85a**, biosynthetically.<sup>25</sup> The Suzuki-Miyaura coupling reaction<sup>8</sup> of 2-bromoindole **80** with indole-2-boronic acid **81** gave the bisindole **82**. Cleavage of the *N*-BOC group in **82** with TFA, protection of the both nitrogen atoms of bisindole with MOMCl and NaH, the Grignard reaction to the formyl group of bisindole, followed by treatment of the resulting secondary alcohol with MOMCl to produce the propargyl MOM-ether **83** in four steps. The propargylindole **83** was subjected to an allene-mediated electrocyclic reaction to yield the indolo[2,3-*a*]carbazole **84**. Oxidation of 6-methylindolocarbazole **84** with DDQ afforded the 6-formylindolocarbazole **85b**, which was an additional oxidation of **85b** with CAN to produce the *N*-MOM-calothrixin B **88**, directly. This result indicates that a quinone-imine structure **86** was formed, and then immediate hydrolysis of an imino group in **86**, followed by an intramolecular condensation occurred to give the indolo[3,2-*j*]phenanthridine **88**. Cleavage of the *N*-MOM group in **88** with provided calothrixin B (**79**). Thus a biomimetic synthesis of calothrixin B (**79**) was achieved through the fully protected indolo[2,3-*a*]carbazole **85b** (Scheme 10).<sup>26b-d</sup>

Scheme 10

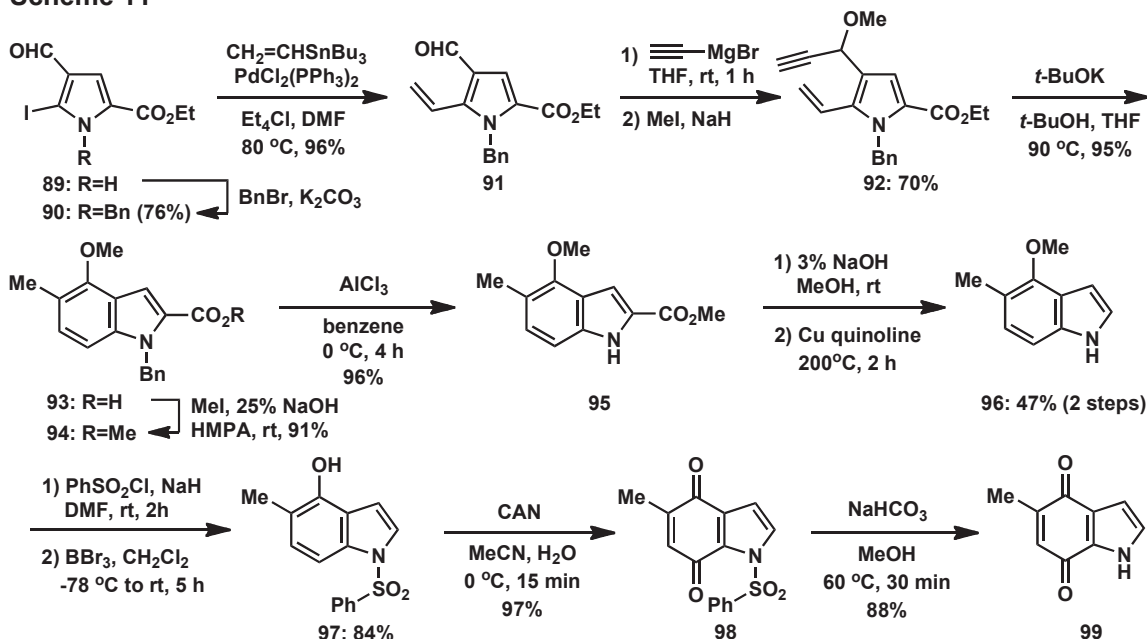


## II-3. Synthesis of indole through an 3- or 2-allenylpyrrole

### II-3-1. Synthesis of 5-methylindole-4,7-quinone

A new antimicrobial indolequinone, 5-methylindole-4,7-quinone (**99**) was isolated from the mid-intestinal gland of the muricid gastropod *Drupella fragum*, together with two related indole-4,7-quinones.<sup>27</sup> We planned a new synthesis of a 4-oxygenated 5-methylindole **96** based on an application of the allene-mediated electrocyclic reaction involving the pyrrole 2,3-bond (Scheme 11). After benzylation of the known pyrrole **89** with benzyl bromide (BnBr), the Pd-catalyzed cross-coupling reaction<sup>11</sup> with

Scheme 11

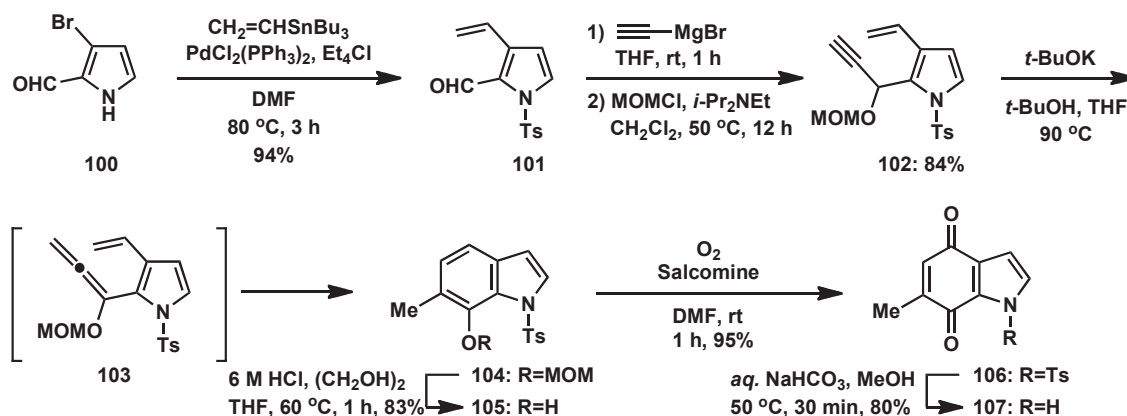


ethenyl tributylstannane afforded the 2-ethenylpyrrole **91**, which was treated with ethynylmagnesium bromide, followed by *O*-methylation of the resulting alcohol with MeI to yield the propargyl methyl ether **92**. The propargyl ether **92** was subjected to an electrocyclic reaction with *t*-BuOK to produce the desired 4-oxygenated indole **93** along with hydrolysis of ester. Cleavage of the benzyl group of **93** with AlCl<sub>3</sub> failed. On the other hand, cleavage of the benzyl group of the ester **94**, derived from **93**, with AlCl<sub>3</sub> provided the *N*-deprotected indole **95**. Hydrolysis of **95**, followed by decarboxylation with Cu afforded the 4-methoxy-5-methylindole (**96**). Direct cleavage of the methyl ether of **96** with BBr<sub>3</sub> failed. The protection of the indole nitrogen atom of **96** with benzenesulfonyl group, followed by treatment of BBr<sub>3</sub> gave the 4-hydroxyindole **97**. Finally, oxidation of **97** with CAN provided the indole-4,7-quinone **98**, which was treated with an aqueous NaHCO<sub>3</sub> to yield 5-methylindole-4,7-quinone (**99**). The synthetic **99** was not consistent with the reported **99**, however, in any aspect.<sup>28a</sup>

### II-3-2. Synthesis of 6-methylindole-4,7-quinone

6-Methylindole-4,7-quinone (**107**) was synthesized to clarify the structure of the natural product, 5-methylindole-4,7-quinone (**99**) isolated from *Drupella fragum* (II-3-1).<sup>27</sup> We also planned a synthesis of 7-oxygenated 6-methylindole **104** through an 3-allenyl-2-propargylpyrrole intermediate **103** (Scheme 12). The Stille reaction<sup>11</sup> of 3-bromopyrrole-2-carbaldehyde (**100**) with ethenyl tributylstannane afforded the 3-ethenylpyrrole **101**. The Grignard reaction of **101** with ethynylmagnesium bromide followed by treatment of the alcohol with MOMCl produced 2-propargyl ether **102**. The propargylpyrrole **102** was subjected to an electrocyclic reaction under the conditions of *t*-BuOK at room temperature to yield the 6-methylindole **104**. Subsequent deprotection of the *O*-MOM group of **104** with 6 M HCl, followed by oxidation of the phenol **105** with salcomine and O<sub>2</sub> gave the indole-4,7-quinone **106**. Finally, removal of

Scheme 12



the *N*-tosyl group of **106** was carried out by an aqueous NaHCO<sub>3</sub> to produce the expected 6-methylindole-4,7-quinone (**107**). The structure of natural indole-4,7-quinone **99**,<sup>26</sup> however, was not identical with either synthetic **99** or **107**. The exact structure of reported **99** is now unclear.<sup>28b</sup>

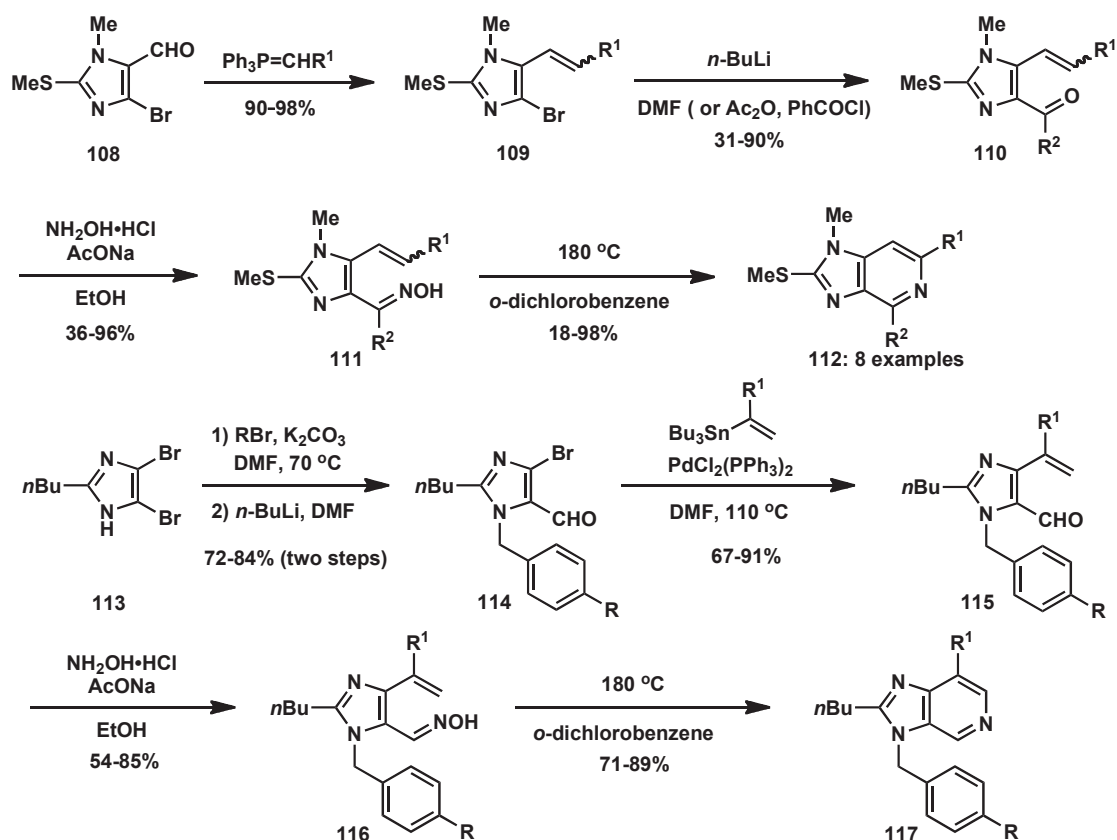
### III. SYNTHETIC STUDIES USING THE THERMAL AZA-ELECTROCYCLIC REACTION

#### III-1. Synthesis of fused pyridine rings by a thermal electrocyclic reaction of an aza $6\pi$ -electron system using an oxime or oxime ether

##### III-1-1. Synthesis of 1*H*- and 3*H*-imidazo[4,5-*c*]pyridines

Synthetic routes to 1*H*- and 3*H*-imidazo[4,5-*c*]pyridines have been developed by an thermal electrocyclic reaction of 1-aza  $6\pi$ -electron systems involving the imidazole 4,5-bond (Scheme 13). For the synthesis of 1*H*-imidazo[4,5-*c*]pyridines **112**, the Wittig reaction of 4-bromo-5-formylimidazole **108** with several alkylidenetriphenylphosphoranes ( $\text{CH}_2=$ ,  $\text{MeCH}=\text{}$ ,  $\text{PhCH}=\text{}$ ) gave the 5-alkenylindoles **109**. Subsequent treatment of 4-bromoimidazoles **109** with *n*-BuLi followed by quenching with several electrophiles [DMF,  $(\text{MeCO})_2\text{O}$ ,  $\text{PhCOCl}$ ] gave the corresponding 4-acylimidazoles **110**, which were treated with hydroxylamine to yield the oximes **111** in an usual manner. The thermal electrocyclic reaction of **111** was carried out at reflux temperature in *o*-dichlorobenzene to produce the proposed 1*H*-imidazo[4,5-*c*]pyridine **112**. Of eight examples attempted, seven were obtained in moderate to good yields, and the eighth was obtained in only 17.5% yield. On the other hand, the synthesis of 3*H*-imidazo[4,5-*c*]pyridine was investigated as follows. Benzilation of the 4,5-dibromoimidazole **113** with benzyl bromide or 4-acetoxybenzyl bromide gave the *N*-benzylimidazoles, which were treated with *n*-BuLi followed by quenching with DMF to yield the 5-formylimidazoles **114**, regioselectively. The

Scheme 13

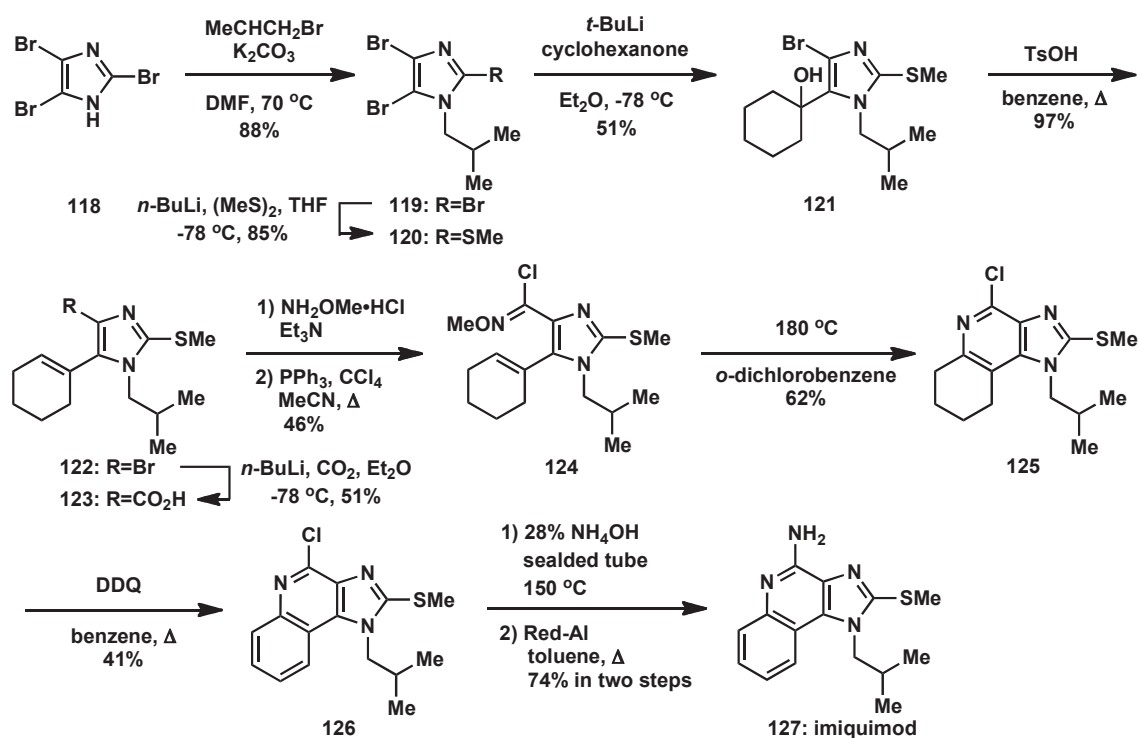


Pd-catalyzed cross-coupling reaction<sup>11</sup> of **114** with alkenyl(tributyl)tin (ethenyl or isopropenyl) afforded the 4-alkenylimidazoles **115**, which were treated with hydroxylamine to give oximes **116**. Four types of oximes **116** were subjected to a thermal electrocyclic reaction to provide 3*H*-imidazo[4,5-*c*]pyridines **117**. In addition, a thermal electrocyclic reaction using the oxime methyl ether was also investigated (72-75% yields). There was almost no difference in this case.<sup>29</sup>

### III-1-2. Synthesis of the imidazo[4,5-*c*]quinoline imiquimod

Imiquimod (**127**), 4-amino-1-isobutyl-1*H*-imidazo[4,5-*c*]quinoline, is a potent inducer of interferon- $\alpha$  in many animal species, as well as humans, and is a potent antiviral and antitumor agent.<sup>30</sup> 2,4,5-Tribromoimidazole (**118**) was alkylated with isobutyl bromide to give the isobutylimidazole **119**, which was converted to the methylsulfanylimidazole **120** by treatment with *n*-BuLi, followed by the addition of MeSSMe. Treatment of **120** with *t*-BuLi and subsequent addition of cyclohexanone

Scheme 14

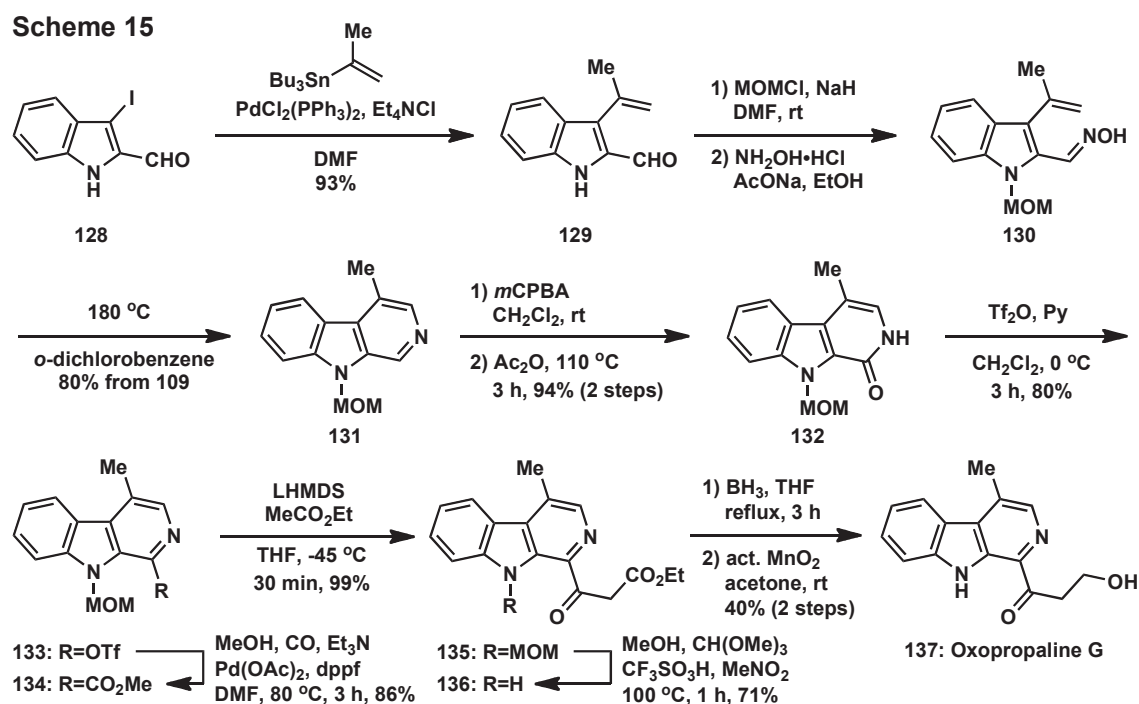


regioselectively produced the cyclohexyl alcohol **121**. Heating **121** in the presence of *p*-TsOH yielded the cyclohexenylimidazole **122**, which was then treated with *n*-BuLi, followed by the introduction of CO<sub>2</sub> gas to afford the corresponding carboxylic acid **123**. Reaction of **123** with hydroxylamine *O*-methyl ether, followed by the addition of PPh<sub>3</sub>-CCl<sub>4</sub> gave the  $\alpha$ -chloro-oxime ether **124**, with an aza 6 $\pi$ -electron system. The electrocyclic reaction of **124** was carried out in *o*-dichlorobenzene, yielding cyclized tetrahydroimidazo[4,5-*c*]quinoline **125**, which was treated with DDQ to provide the imidazo[4,5-*c*]pyridine **126**. Finally, treatment of **126** with conc. NH<sub>4</sub>OH in a sealed tube followed by

desulfurization with Red-Al afforded imiquimod (**127**) (Scheme 14).<sup>31</sup>

### III-1.3. Synthesis of the $\beta$ -carboline alkaloids oxopropalines G and D

The novel cytotoxic  $\beta$ -carbolines, oxopropalines D (**141b**) and G (**137**) were isolated from *Streptomyces* sp. G324 together with three related oxopropalines,<sup>32</sup> which produces lavendamycin. Initially, 1-methoxycarbonyl-4-methyl- $\beta$ -carboline (**134**) was synthesized as a common key compound (Scheme 15). The Pd-catalyzed cross-coupling reaction<sup>11</sup> between 3-iodoindole-2-carbaldehyde (**128**) and isopropenyl tributylstannane gave the isopropenylindole **129**. The *N*-protection of **129** with MOMCl followed by treatment with hydroxylamine produced the oxime **130**, which was subjected to a thermal electrocyclic reaction to yield the  $\beta$ -carboline nucleus **131**. Treatment of **131** with *m*CPBA followed by heating in Ac<sub>2</sub>O yielded the 1-hydroxy- $\beta$ -carboline **132**, which was treated with Tf<sub>2</sub>O to furnish the triflate **133**. Methoxycarbonylation of **133** with CO and MeOH in the presence of Pd(OAc)<sub>2</sub> and 1,1'-bis(diphenylphosphino)ferrocene (dppf) provided the common key compound **134**. Nucleophilic addition of **134** with the acetate carbanion afforded the *N*-MOM- $\beta$ -keto ester **135**. The *N*-MOM deprotected  $\beta$ -carboline **136** was successfully obtained by heating in MeOH, CH(OMe)<sub>3</sub>, CF<sub>3</sub>SO<sub>3</sub>H, and MeNO<sub>2</sub>.<sup>33</sup> Reduction of **136** with diborane followed by selective oxidation of the resulting 1,3-diol with act. MnO<sub>2</sub> gave oxopropaline G (**137**).<sup>34a,b</sup>

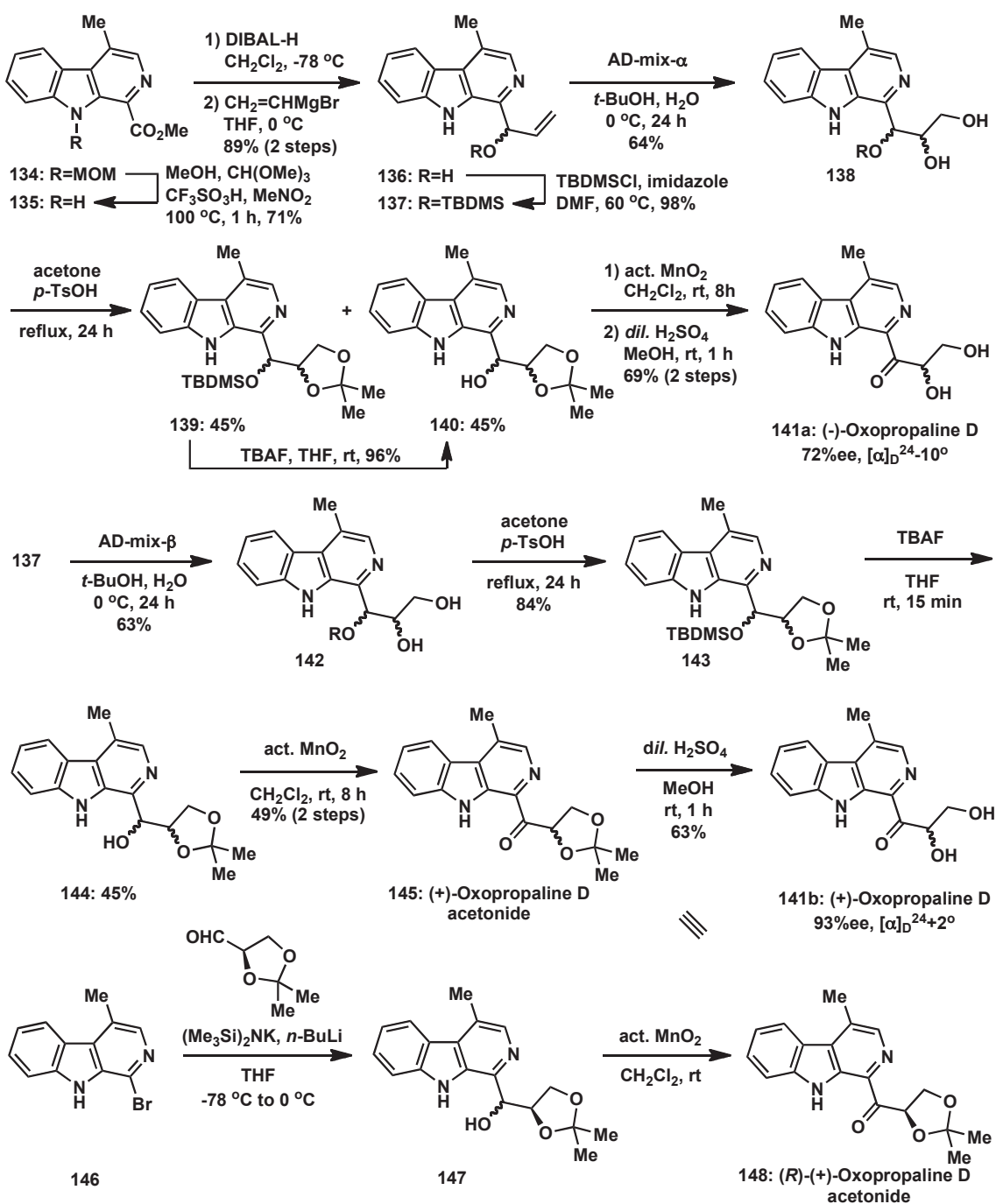


Furthermore, the synthesis of oxopropaline D (**141b**) was attempted using **134** (Scheme 16). The *N*-MOM carbazole **134** was converted to **135** using the our procedure.<sup>33</sup> Reduction of **135** with DIBAL-H afforded the aldehyde, which was treated with vinylmagnesium bromide followed by silylation of the resulting



alcohol **136** with TBDMSCl to obtain the allyl silyl ether **137**. The allyl ether **137** was treated with AD-mix- $\alpha$  using the Sharpless oxidation<sup>35</sup> to produce the 1,2-diol **138**, which was then converted to the acetonide **139** along with its desilylated acetonide **140**. Compound **139** was converted to **140** with TBAF. Oxidation of the alcohol **140** with act. MnO<sub>2</sub>, followed by treatment of the resulting ketone with dil. H<sub>2</sub>SO<sub>4</sub> provided (-)-oxopropaline D (**141a**). On the other hand, the allyl ether **137** was oxidized with AD-mix- $\beta$  to produce the other 1,2-diol **142**, which was converted to the acetonide **143**. Similarly, removal of the TBDMS group of **143** followed by oxidation of the alcohol furnished the ketone **144**. The keto-acetonide **144** was treated with dil. H<sub>2</sub>SO<sub>4</sub> to give (+)-oxopropaline D (**145**). The keto-acetonide **144** was treated with dil. H<sub>2</sub>SO<sub>4</sub> to give (+)-oxopropaline D (**145**). The specific rotation

Scheme 16

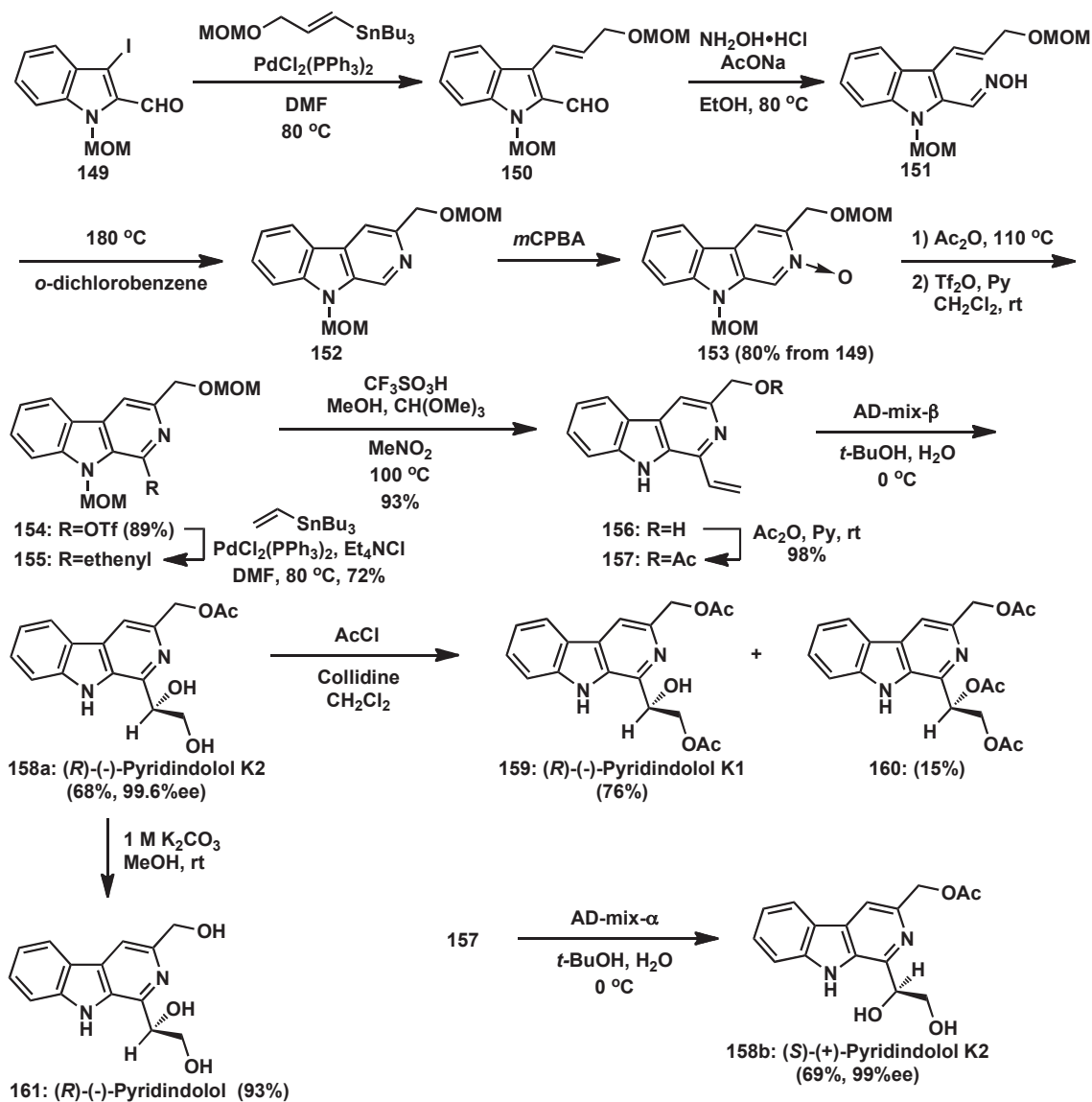


of **141b** showed the same direction of rotation and approximate value as that of the natural product.<sup>34a,b</sup> To determine the absolute configuration of **145** and **141b**, treatment of the 1-bromo- $\beta$ -carboline **146**, derived from **132**, with  $[(\text{Me})_3\text{Si}]_2\text{NK}$  and  $n\text{-BuLi}$  followed by the reaction with (*R*)-glyceraldehyde acetonide produced the alcohol **147**, which was oxidized with act.  $\text{MnO}_2$  to yield (*R*)-(+)-oxopropaline D acetonide **148**. The HPLC data and the specific rotation of **148** were identical with those of synthetic **145**. The absolute stereochemistry of the C-11 position of natural (+)-oxopropaline D (**141b**) was determined to be the *R*-configuration.<sup>34c</sup>

### III-1-4. Synthesis of $\beta$ -carboline alkaloids, (*R*)-(-)-pyridindolols

Pyridindolol (**161**) was initially isolated from *Streptomyces alboverticillatus* as a  $\beta$ -galactosidase inhibitor.<sup>36a</sup> Three pyridindolols containing the glucoside were also isolated from *Streptomyces parvulus*, strain Tu2480.<sup>36b</sup> Furthermore, pyridindolols K1 (**159**) and K2 (**158a**) were isolated from *Streptomyces* sp. K93-0711 together with pyridindolol (**161**). The stereochemistry of the C-14 position of all pyridindolols was reported to be in an *R*-configuration.<sup>36c</sup> The Pd-catalyzed cross-coupling reaction<sup>11</sup> of *N*-MOM-3-iodoindole **149** with tributyl[3-(MOMoxy)prop-1-en-1-yl]stannane gave the 3-alkenylindole **150**. After the aldehyde **150** was converted to the oxime **151**, it was subjected to a thermal electrocyclic reaction to produce the  $\beta$ -carboline **152**. Subsequent oxidation of **152** with *m*CPBA afforded the  $\beta$ -carboline *N*-oxide **153**. Synthesis of compound **153** was also investigated using Sakamoto's procedure<sup>37</sup> through the ring closure of the 3-alkynylindole-2-aldoxime. Next, heating **153** with  $\text{Ac}_2\text{O}$  at reflux temperature, followed by treatment of the resulting 1-hydroxy- $\beta$ -carboline with  $\text{Tf}_2\text{O}$  and pyridine, afforded the triflate **154**. The triflate **154** was used in the Pd-catalyzed cross-coupling reaction<sup>11</sup> with vinyl tributylstannane to give the 1-ethenyl- $\beta$ -carboline **155**. Deprotection of the *N*-MOM-group of **155** with our reported procedure<sup>33</sup> yielded the ethenyl- $\beta$ -carboline **156**. After acetylation of **156** with  $\text{Ac}_2\text{O}$ , the Sharpless asymmetric dihydroxylation<sup>35</sup> of **157** with AD-mix- $\alpha$  provided (*S*)-(+)-pyridindolol K2 (**158b**). By contrast, the reaction of **157** with AD-mix- $\beta$  was carried out in a similar way to produce (*R*)-(-)-pyridindolol K2 (**158a**). In addition, selective acetylation of **158a** afforded (*R*)-(-)-pyridindolol K1 (**159**) along with the triacetate **160**. On the other hand, hydrolysis of **158a** with  $\text{K}_2\text{CO}_3$  provided pyridindolol (**161**). Total syntheses of the three pyridindolols together with (*S*)-(+)-enantiomer **158b** were achieved (Scheme 17).<sup>38</sup>

Scheme 17

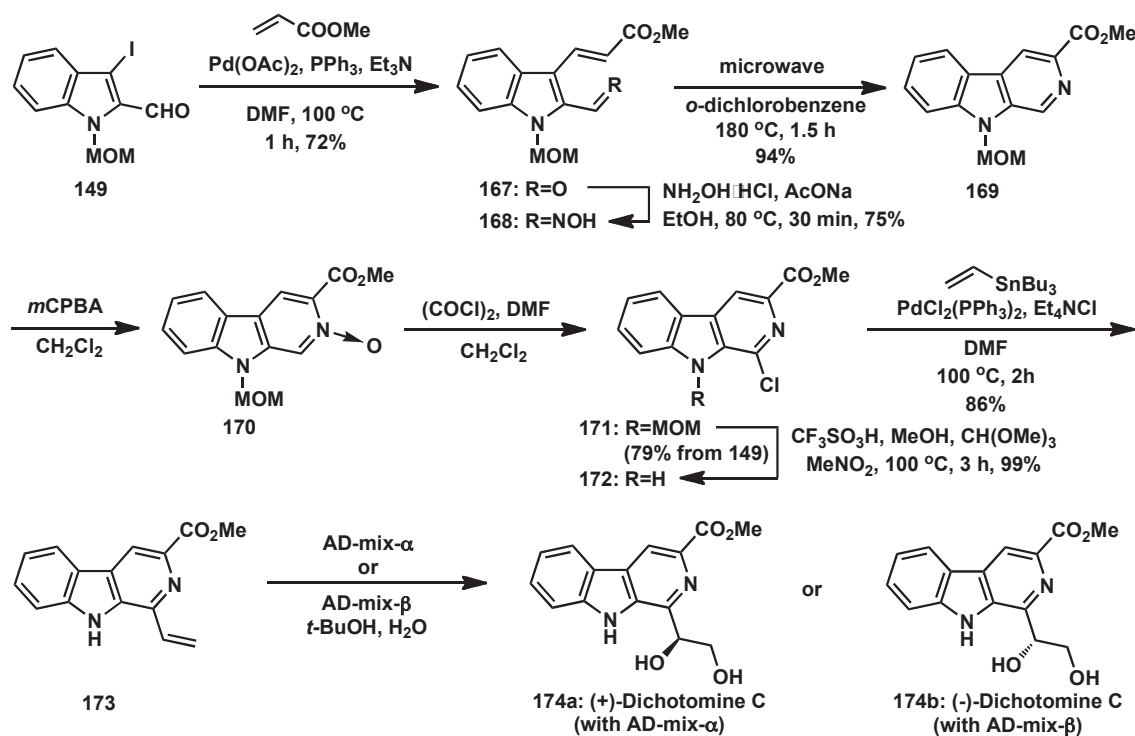


### III-1-5. Synthesis of the $\beta$ -carboline alkaloid, dichotomine C

(-)-Dichotomine C (**174b**) was isolated from *Stellaria dichotoma* along with five related  $\beta$ -carboline alkaloids. The absolute configuration of the C14 position in dichotomine C (**174b**) was determined to be the *S*-configuration.<sup>39</sup> The required  $\beta$ -carboline **169** was prepared from 3-iodoindole **149** (Scheme 18). The Heck reaction<sup>40</sup> between the iodoindole **149** and methyl acrylate gave the 3-alkenylindole-2-carbaldehyde **167**. Subsequent treatment of hydroxylamine produced the oxime **168**, which was subjected to a microwave (MW)-assisted thermal electrocyclic reaction to yield the methyl  $\beta$ -carboline-3-carboxylate **169**. Subsequently, treatment of **169** with *m*CPBA followed by chlorination with oxalyl chloride yielded the *N*-MOM-1-chloro- $\beta$ -carboline **171**. Cleavage of the *N*-MOM group of **171** with our reported procedure<sup>33</sup> afforded the 1-chloro- $\beta$ -carboline **172**. The 1-ethenyl- $\beta$ -carboline **173** was synthesized from **172** with ethenyl(tributyl)tin by the Stille reaction.<sup>11</sup> Finally, asymmetric

dihydroxylations<sup>35</sup> of **173** with AD-mix- $\alpha$  or AD-mix- $\beta$  were carried out to provide the corresponding (-)-dichotomine C (**174b**) or (+)-dichotomine C (**174a**), respectively,<sup>41</sup> contrary to the Sharpless rule.<sup>35</sup>

Scheme 18

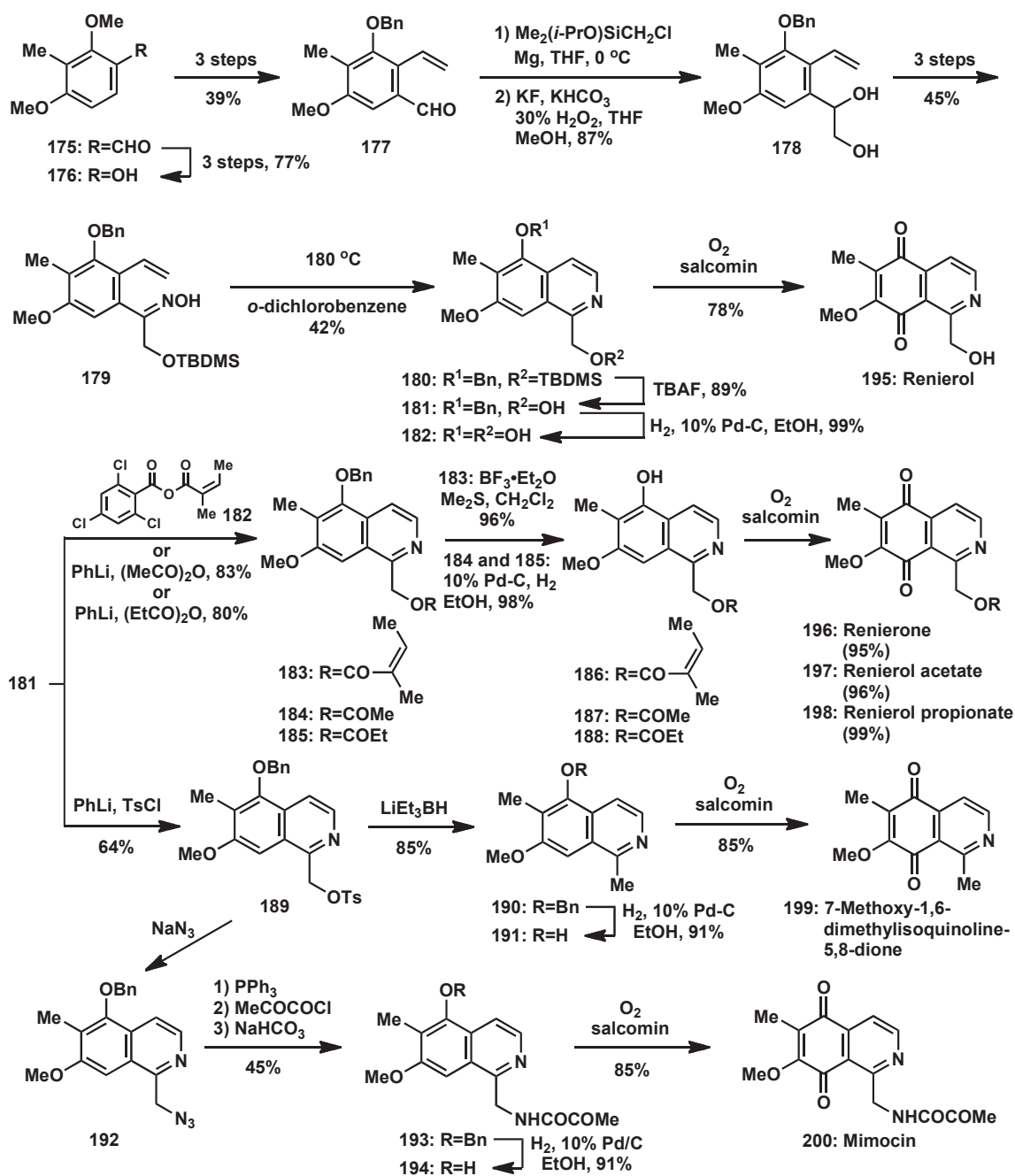


### III-1-6. Synthesis of isoquinoline-5,8-quinone alkaloids, renierol and related natural products

Renierone (**196**) was isolated from the major metabolite of *Reniera* sp.<sup>42</sup> Mimocin (**200**), isolated from a metabolite of *Streptomyces lavendulae*, contains a pyruvamide in place of the angelate ester side chain of **196**.<sup>43a</sup> Renierol (**195**) was isolated from the hard blue sponge *Xestospongia caycedoi*.<sup>43b</sup> Further studies of the metabolites of *Reniera* sp. have resulted in the isolation of 7-methoxy-1,6-dimethylisoquinoline-5,8-dione (**199**),<sup>42b,43c</sup> which was also found in a blue Phillipin marine sponge of the genus *Xestospongia* sp.<sup>43b</sup> In addition, renierol acetate (**197**) and renierol propionate (**198**) were isolated from the marine sponge *Xestospongia* sp. and its associated nudibranch *Jorunna funebris*.<sup>44</sup> For the synthesis of key compound **181** (Scheme 19), treatment of benzaldehyde **175** with  $\text{BBr}_3$ , followed by conversion of the 2-hydroxybenzaldehyde into the benzyl ether, which was subjected to the Baeyer-Villiger reaction to produce the phenol **176**. The Duff reaction of **176** followed by treatment of the resulting 2-hydroxybenzaldehyde with  $\text{Tf}_2\text{O}$  gave the triflate, which was carried out by the Stille reaction of the triflate with ethenyl tributylstannan to yield the 2-ethenylbenzaldehyde **177**. The Grignard reaction of **177** with dimethylisopropylsilylmethylmagnesium chloride, followed by treatment with  $\text{KF}$  and  $\text{H}_2\text{O}_2$ , afforded the 1,2-diol **178**. Selective protection of **178** with  $\text{TBDMSCl}$ , followed by oxidation with  $\text{PCC}$ , gave the ketone, which was treated with hydroxylamine to produce the ketoxime **179**.

The oxime **179** was subjected to a thermal electrocyclic reaction to furnish the 5-benzyloxyisoquinoline **180**. Although the electrocyclic reaction of the highly substituted substrate **179** also proceeded, the yield of **180** was only marginally better than that of the simple 2-alkenylbenzaloxime.<sup>2</sup> Deprotection of the TBDMS group of **180** with TBAF provided the desired 5-benzyloxy-1-hydroxymethylisoquinoline **181** as the common precursor with the appropriate substituents. For the next stage, precursor **181** was converted to the corresponding esters, angelate **183**, acetate **184**, and propionate **185** by treatment of **181** with PhLi, followed by addition of the mixed anhydride **182**, Ac<sub>2</sub>O, and (EtCO)<sub>2</sub>O, respectively.

## Scheme 19

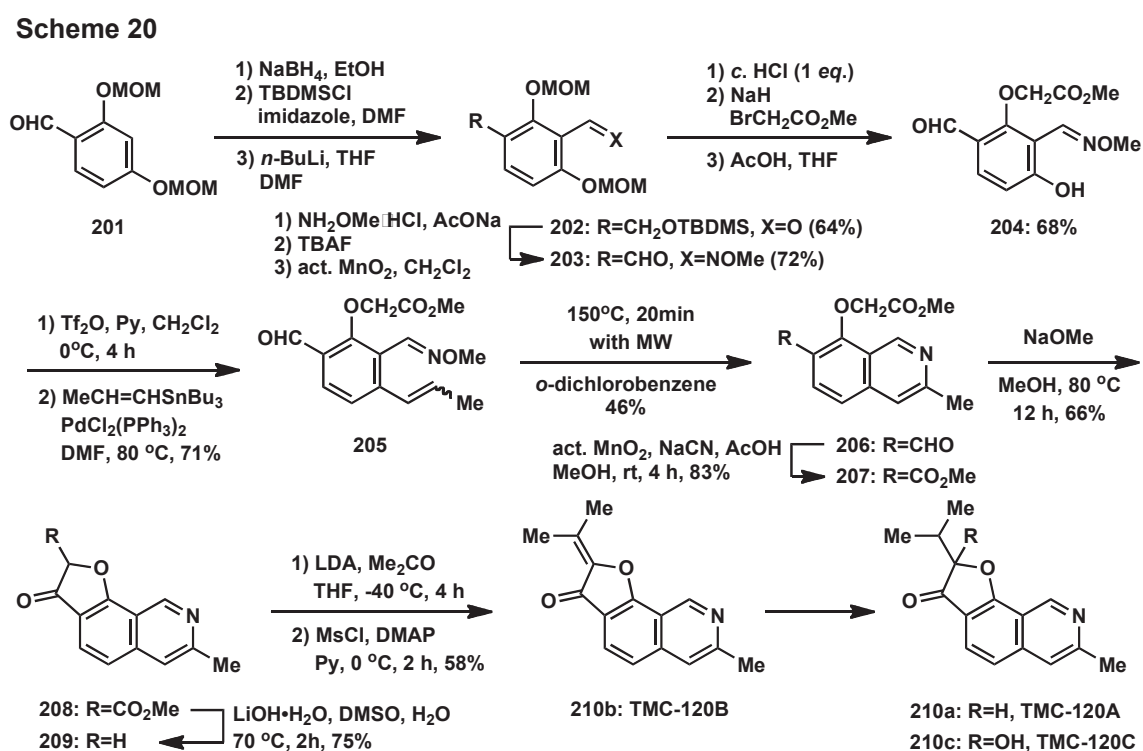


Furthermore, treatment of **181** with PhLi, followed by addition of *p*-toluenesulfonyl chloride gave the

tosylate **189**, which was reduced with  $\text{LiEt}_3\text{BH}$  to yield the 1-methylisoquinoline **191**. In addition, the nucleophilic substitution reaction of **189** with  $\text{NaN}_3$  produced the azide derivative **192**, which was treated with  $\text{PPh}_3$  *in situ*, followed by addition of pyruvoyl chloride to furnish the 1-pyruvoylaminomethylisoquinoline **194**. Sequential cleavages of the benzyl groups of **181**, **184**, **185**, **190**, and **193** were carried out by hydrogenolysis to give the corresponding phenols **182**, **187**, **188**, **191**, and **194**, respectively. Although debenzoylation of **183** with hydrogenolysis failed, cleavage of the ether of **183** was subjected to the Fuji's procedure<sup>45</sup> to successfully produce the phenol **186**. At the final stage, the 5-hydroxyisoquinolines **182**, **186-188**, **191**, and **194** were oxidized by salcomine with  $\text{O}_2$  (or CAN) to provide the corresponding isoquinoline-5,8-quinone alkaloids **195-200** in excellent yields.<sup>46</sup>

### III-1-7. Synthesis of the furo[3,2-*h*]isoquinoline alkaloids TMC-120B and A

Furo[3,2-*h*]isoquinoline alkaloid TMC-120B (**210b**) was isolated from *Aspergillus ustus* TMC1118, together with TMC-120A (**210a**) and TMC-120C (**210c**).<sup>47</sup> The aldehyde **202** was prepared in three steps from 2,4-diMOMoxybenzaldehyde (**201**) (Scheme 20). The subsequent benzaldehyde **203** was synthesized in three steps from **202**. The selective cleavage of MOM-ether group of **203** with conc. HCl (one equiv.) afforded the 2-hydroxybenzaldehyde, which was converted to the ether with methyl bromoacetate and NaH. Cleavage of the 4-MOM group of the ether with an aqueous AcOH produced the 4-hydroxybenzaldehyde **204**. The phenol **204** was treated with  $\text{Tf}_2\text{O}$ , and then the Pd-catalyzed cross-coupling reaction<sup>11</sup> of the triflate with tributyl(1-propenyl)tin yielded the 2-alkenylbenzaldoxime **205**. The subsequent thermal electrocyclic reaction of the oxime ether **205** was carried out under both

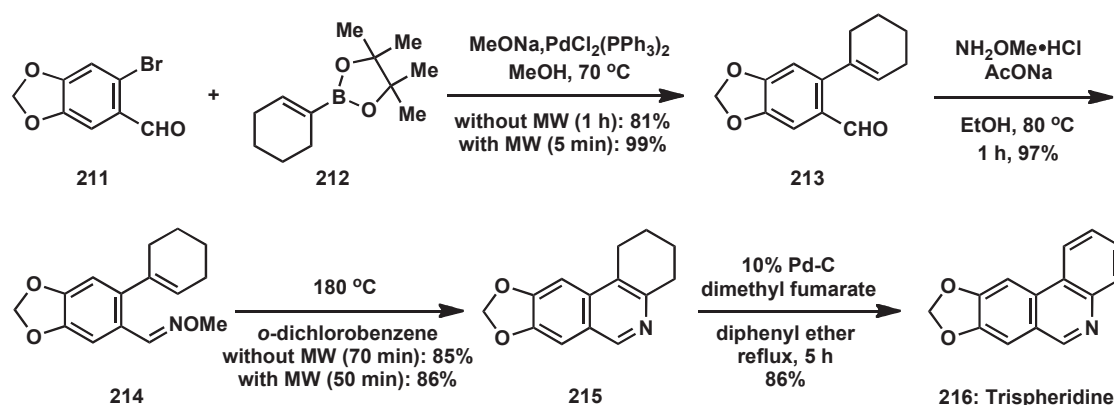


conventional conditions and MW-irradiation to provide the 3,7,8-trisubstituted isoquinoline **206**. The MW-irradiation condition was slightly more effective than the conventional condition. The 7-formylisoquinoline **206** was converted to the methyl ester **207**, which was cyclized with NaOMe to produce the  $\beta$ -ketoester **208**, and then **208** was treated with LiOH to give the furanone **209**. The furanone **209** was treated with LDA and acetone, and subsequent treatment with MsCl and DMAP provided TMC-120B (**210b**). **210b** was converted to TMC-120A (**210a**) with 10% Pd-C and H<sub>2</sub>.<sup>48</sup>

### III-1-8. Synthesis of the phenanthridine alkaloid trispheridine

The phenanthridine alkaloid trispheridine (**216**) was found in a member of the *Amaryllidaceae* plant family.<sup>49</sup> The required 2-cyclohexenylalldoxime **214** was prepared as follows (Scheme 21). The Suzuki-Miyaura reaction<sup>8</sup> of 2-bromopiperonal (**211**) with cyclohexenylboronic acid pinacol ester (**212**) was carried out under conditions of PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> and NaOMe at 70 °C to give the cyclohexenylbenzaldehyde **213**. This reaction was also attempted under MW-irradiation for 5 min to produce **213** in excellent yield. Subsequent treatment of **213** with NH<sub>2</sub>OMe afforded the required oxime ether **214**, which was subjected to a thermal electrocyclic reaction under both MW-assisted and conventional conditions to yield the tetrahydrophenanthridine **215**. The yield and reaction rate of this reaction were promoted by the MW irradiation. Finally, heating **215** with 10% Pd-C in Ph<sub>2</sub>O in the presence of diethyl fumarate provided trispheridine (**216**).<sup>50</sup>

Scheme 21

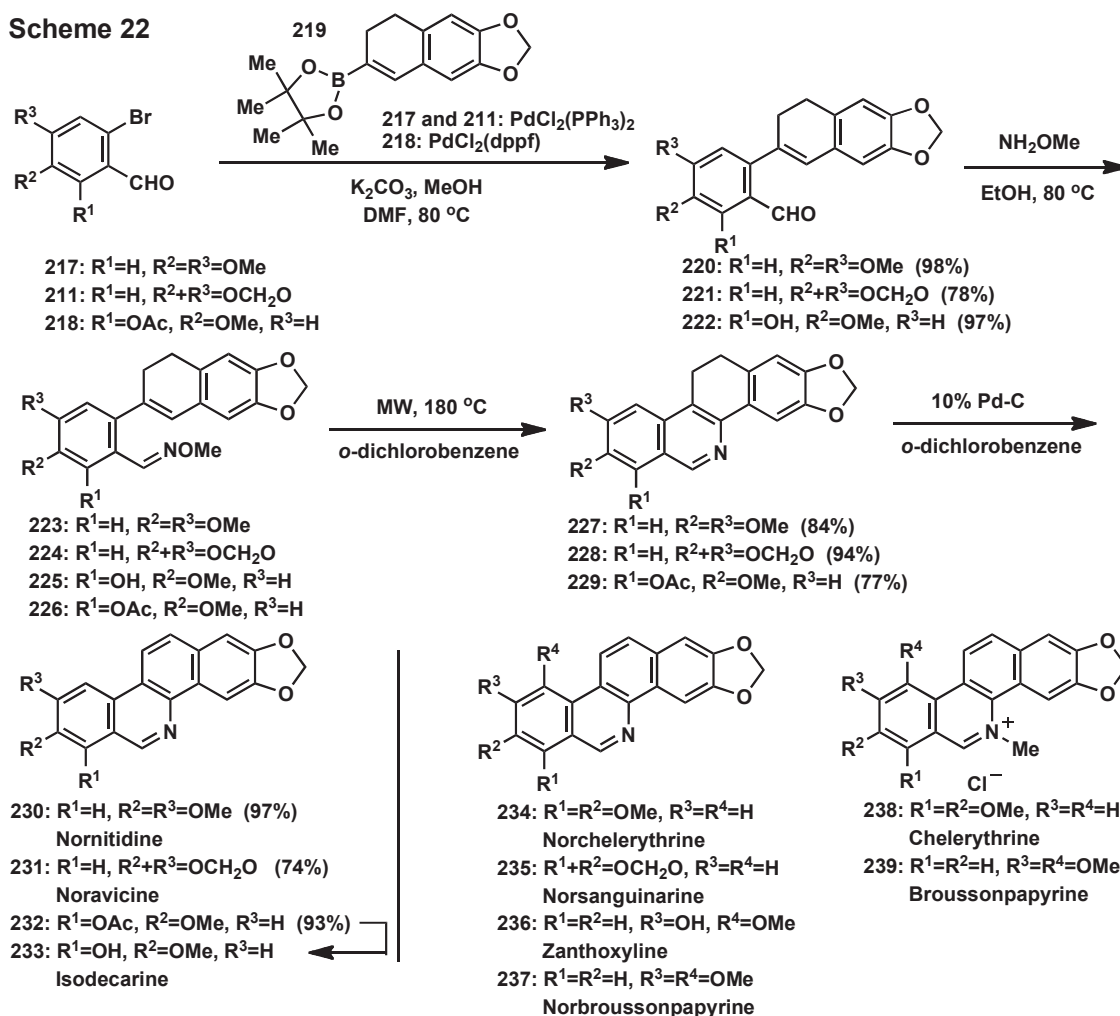


### III-1-9. Synthesis of benzo[*c*]phenanthridine alkaloids and structural revision of broussonpapyrine

Benzo[*c*]phenanthridine alkaloids were isolated from the Rutaceae, Papaveraceae, and Fumariaceae plants.<sup>51</sup> We planned a bond formation of C4b and N5 using a microwave-assisted electrocyclic reaction for construction of the tetracyclic benzo[*c*]phenanthridine nucleus (Scheme 22). The Suzuki-Miyaura reaction<sup>8</sup> of 2-bromobenzaldehydes **217**, **211**, and **218** with the pinacol borate **219** (prepared from 2-allyl-4,5-methylenedioxyphenol in seven steps) proceeded smoothly to give the

2-cycloalkenylbenzaldehydes **220**, **221**, and deacetylated **222**, which were converted to the oxime ethers **223**, **224**, and **225**, respectively. The oxime ethers **223**, **224**, and acetylated **226** were subjected to a thermal electrocyclic reaction under MW-irradiation to yield the corresponding 11, 12-dihydrobenzo[*c*]phenanthridines **227**, **228**, and **229**. Finally, the dihydro-compounds **227**, **228**, and **229** were oxidized by refluxing with 10% Pd-C in *o*-dichlorobenzene to give norнитidine (**230**), noravicine (**231**), and *O*-acetylisodecarine **232**, respectively. Hydrolysis of the acetyl group of **232** with KHC<sub>3</sub>O<sub>3</sub> provided isodecarine (**233**).<sup>52a</sup> Similarly, norchelerythrine (**234**), norsanguinarine (**235**), zanthoxyline (**236**), and norbroussonpapyrine (**237**) were also synthesized. Although the structure of synthetic zanthoxyline (**236**) was consistent with zanthoxyline (**236**) synthesized previously by the Abe group,<sup>53a</sup> the structure of the reported zanthoxyline by the Morel group<sup>53b</sup> was revised to the structure of decarine.<sup>53a</sup> The structure of the synthetic broussonpapyrine (**239**) was not consistent with the reported structure **239** by the Qin group.<sup>53c</sup> The structure of the reported broussonpapyrine (**239**) was revised to the structure of chelerythrine (**238**) based on comparison of the <sup>1</sup>H- and <sup>13</sup>C-NMR spectra.<sup>52</sup>

Scheme 22

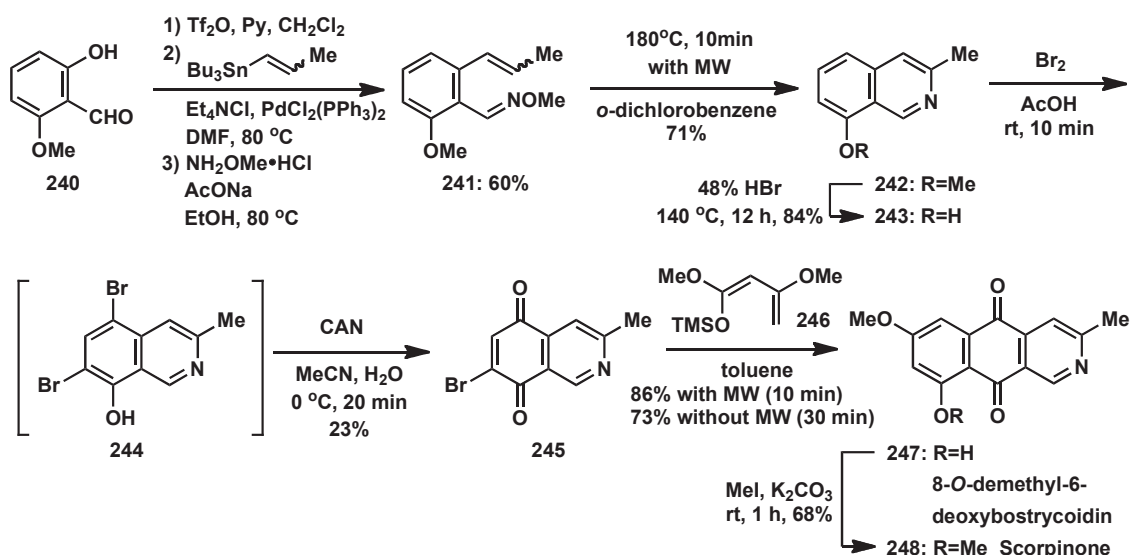




### III-1-10. Synthesis of the 2-azaanthraquinone alkaloid scorpinone

The 2-azaanthraquinone alkaloid scorpinone (**248**) was isolated from the mycelium of a *Bispora*-like tropical fungus.<sup>54</sup> The 2-propenylbenzaloxime **241** was prepared from 2-hydroxy-6-methoxybenzaldehyde (**240**) in three steps (Scheme 23). Treatment of **240** with Tf<sub>2</sub>O and pyridine afforded the triflate. The Stille reaction<sup>11</sup> of the resulting triflate with tributyl(1-propenyl)tin produced the 2-propenylbenzaldehyde, which was treated with hydroxylamine methyl ether to yield the aldoxime methyl ether **241**. A thermal electrocyclic reaction of **241** was carried out in *o*-dichlorobenzene under MW-irradiation to provide the isoquinoline **242** along with the loss of methanol. This reaction of **241** was also attempted under the conventional conditions, but the isoquinoline **242** was obtained in low yield together with a byproduct. Cleavage of methyl ether of **242** with 48% HBr afforded the 8-hydroxyisoquinoline **243**. Bromination of **243** was performed to give the 5,7-dibromoisoquinoline **244**, which was immediately oxidized with CAN to yield the isoquinoline-5,8-dione **245**. Subsequent Diels-Alder reaction of **245** with the diene **246** gave the known 6-deoxybostrycoidine (**247**) with the elimination of a methoxy group. The use of MW-irradiation was more effective than the conventional condition for improving the yield and decreasing the reaction time. Alkylation of **247** with MeI and K<sub>2</sub>CO<sub>3</sub> provided scorpinone (**248**).<sup>55</sup>

Scheme 23



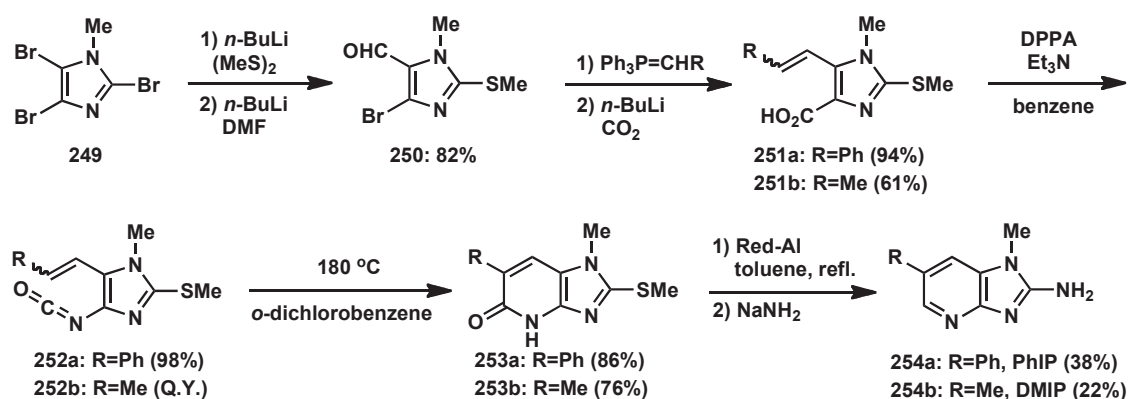
### III-2. Synthesis of fused pyridine rings by a thermal electrocyclic reaction of an aza 6π-electron system using an isocyanate

#### III-2-1. Synthesis of the imidazo[4,5-*b*]pyridines PhIP and DMIP

Mutagens, 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP) (**254a**) and 2-amino-1,6-dimethylimidazo[4,5-*b*]pyridine (DMIP) (**254b**) were isolated from cooked beef and fried Norwegian sausage,<sup>56</sup> along with the other mutagenic heterocyclic amines. We planned the synthesis of an

imidazo[4,5-*b*]pyridin-5(4*H*)-one **253** by a thermal electrocyclic reaction of 5-alkenylimidazole-4-isocyanate **252** (Scheme 24), according to the modified Eroy's pyrido-annulation.<sup>57</sup> Treatment of 1-methyl-2,4,5-tribromoimidazole (**249**) with *n*-BuLi followed by the addition of dimethyldisulfide gave the 2-methylsulfanylimidazole, which was treated in a similar way with *n*-BuLi followed by the addition of DMF to yield the 5-formylimidazole **250**. The Wittig reaction of **250** with alkyltriphenylphosphorane (R=Ph and Me) produced 5-alkenylimidazoles, and then treatment of 5-alkenylimidazoles with *n*-BuLi followed by the addition of gaseous CO<sub>2</sub> afforded the 4-carboxylic acids **251a** and **251b**, respectively. Carboxylic acids **251a** and **251b** were heated in benzene with DPPA and Et<sub>3</sub>N under the Curtius conditions to give the relatively stable isocyanates **252a** and **252b**. The isocyanates **252a** and **252b** were subjected to a thermal electrocyclic reaction to produce the expected pyridones **253a** and **253b**. Finally, reduction of **253a** and **253b** with Red-Al followed by replacement of the methylsulfanyl group with NaNH<sub>2</sub> provided PhIP (**254a**) and DMIP (**254b**), respectively.<sup>58</sup>

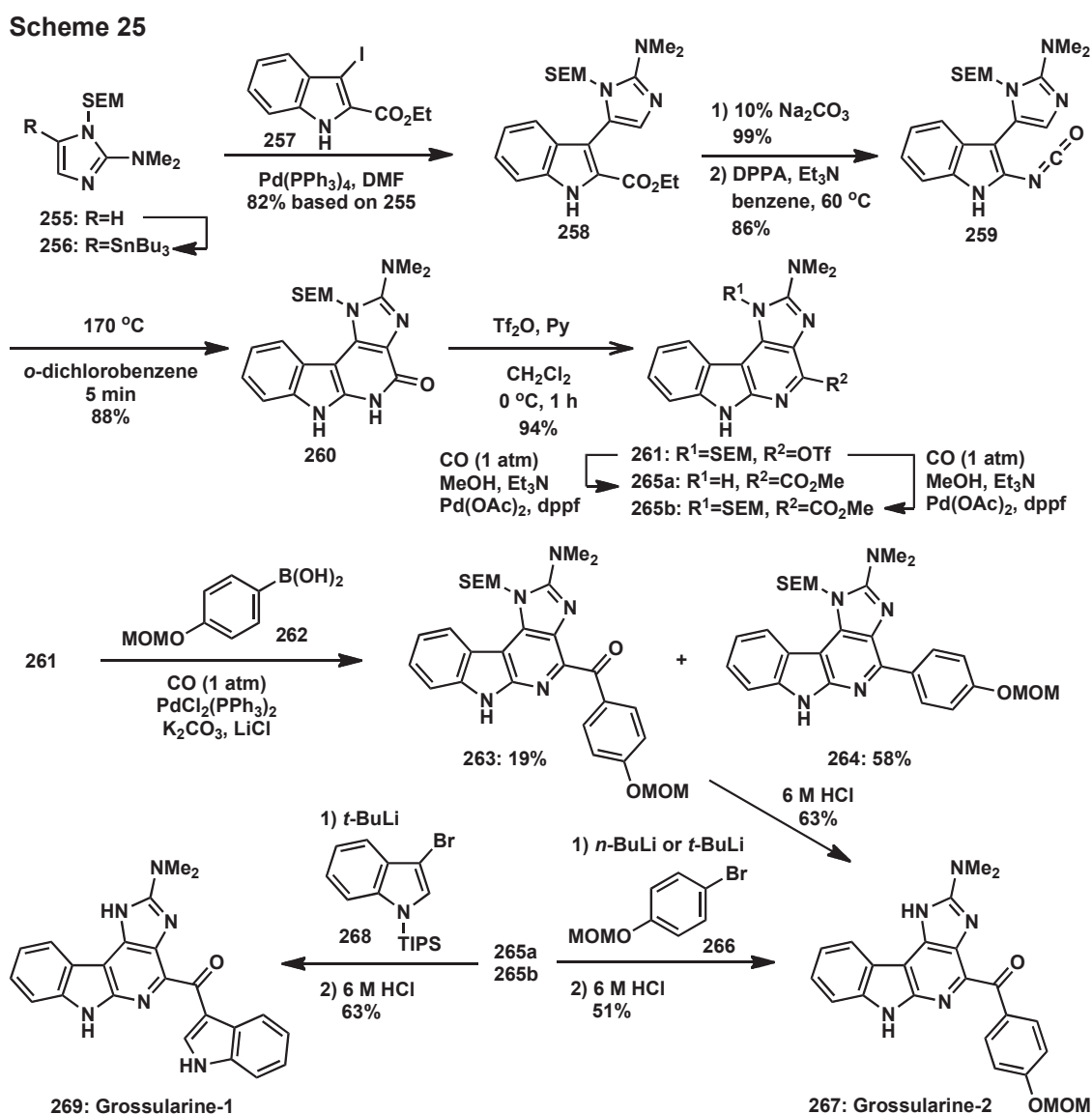
Scheme 24



### III-2-2. Synthesis of the imidazo- $\alpha$ -carboline alkaloids, grossularines-1 and -2

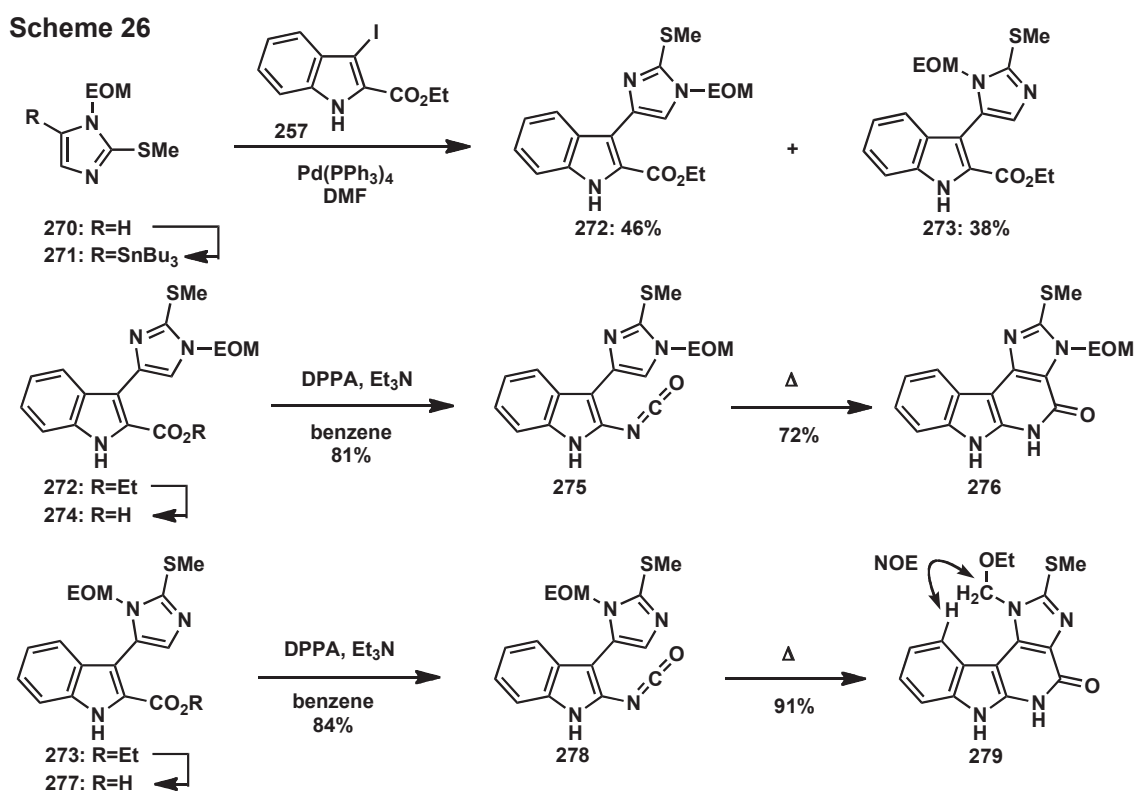
Grossularines-1 (**269**) and -2 (**267**) were isolated from *dendrodoa grossularia* (Stylidae), a tunicate collected in Britany.<sup>59</sup> These antitumor substances are the first example of naturally occurring pyrido[2,3-*b*]indole. Treatment of the *N*-SEM-imidazole (**255**) with *t*-BuLi, followed by the addition of tributyltin chloride, gave the stannylimidazole **256**, which was subjected to the Pd-catalyzed cross-coupling reaction<sup>11</sup> to yield the 3-(5-imidazolyl)indole **258**. Hydrolysis of **258** with Na<sub>2</sub>CO<sub>3</sub> yielded the carboxylic acid, which was treated with DPPA at 60 °C to provide the isocyanate **259** as the required aza 6 $\pi$ -electron system. The thermal electrocyclic reaction of **259** was carried out at 170 °C for 5 min to produce the tetracyclic pyrido[2,3-*b*]indole **260**. Furthermore, **260** was converted into the triflate **261**. The three-component Pd-catalyzed cross-coupling reaction<sup>8</sup> between the triflate **261**, CO, and 4-MOMoxyphenylboronic acid (**262**) was carried out in anisole at 80 °C to provide the 2-benzoylpyrido[2,3-*b*]indole **263** along with the 2-phenylpyrido[2,3-*b*]indole **264** as a major product

(Scheme 25). Subsequent hydrolysis of the *N*-SEM group of **263** with dil. HCl gave grossularine-2 (**267**). A similar application of this reaction to the synthesis of grossularine-1 (**269**), however, failed. In addition, triflate **261** was converted into the methyl esters, either *N*-deprotected **265a** or **265b**, by a Pd-catalyzed carbonylation, according to the Ortar' procedure,<sup>60</sup> depending upon the amount of Et<sub>3</sub>N. The nucleophilic addition to the methyl ester **265a** or **265b** with phenyllithium **266**, followed by hydrolysis with dil. HCl, gave the desired grossularine-2 (**267**) from both substrates. Furthermore, the reaction to methyl ester **265a** or **265b** with 3-indolylithium **268**, followed by hydrolysis with dil. HCl, also provided grossularine-1 (**269**) in a similar way. This approach based on the thermal electrocyclic reaction of an aza 6π-electron system provided an effective route to produce the imidazo[4',5':3,4]pyrido[2,3-*b*]indole nucleus.<sup>61</sup>



### III-2-3. Synthesis of imidazo- $\alpha$ -carbolines through an anomalous Stille reaction

During the course of our studies toward the total synthesis of grousularines-1 (**269**) and -2 (**267**),<sup>61</sup> we required 3-imidazolylindole **273** for a tetracyclic  $\alpha$ -carboline framework (Scheme 26). 5-Stannylimidazole (**271**) was prepared from 1-ethoxymethyl(EOM)-5-bromo-2-methylsulfanylimidazole (**270**) by a bromine-lithium exchange reaction with *n*-BuLi followed by treatment with tributyltin chloride. The Pd-catalyzed cross-coupling reaction<sup>11</sup> of **271** with 3-iodoindole **257** was carried out in DMF at 120 °C to tentatively give two separable imidazolylindoles **272** and **273**. To determine the structures of **272** and **273**, both products independently led to tetracyclic  $\alpha$ -carbolines. Hydrolysis of esters **272** and **273** followed by Curtius rearrangement using DPPA yielded isocyanates **275** and **278**, which were subjected to thermal electrocyclic reaction to provide  $\alpha$ -carbolines **276** and **279**, respectively. The two structures were determined by NOE experiments to be **276** and **279**, respectively. Thus, this reaction proceeds by way of not only *ipso*-substitution but also *cine*-substitution reaction, and seems to be the first example of *cine* substitution of heteroarylstannane. The Stille reaction of *N*-SEM-imidazole **256** with 3-iodoindole **257** fortunately proceeded normally, however, to provide the desired product (III-2-2).<sup>62</sup>

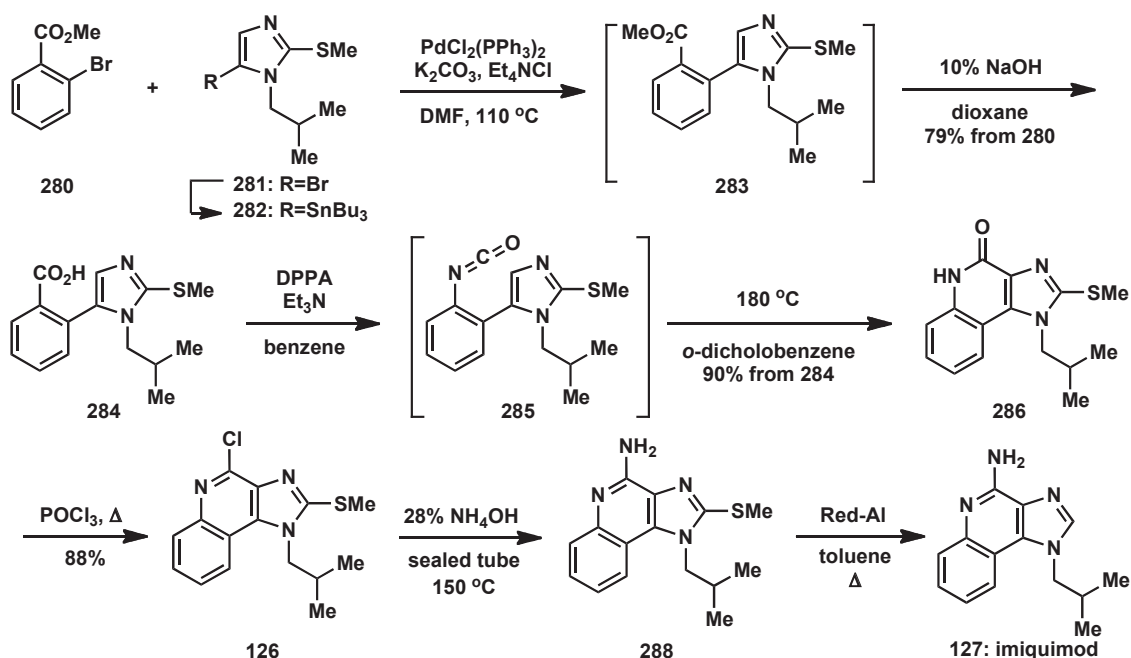


### III-2-4. Synthesis of the imidazo[4,5-*c*]quinoline imiquimod through isocyanate

Imiquimod (**127**) was also synthesized by constructing the imidazo[4,5-*b*]quinoline ring **286** based on the thermal electrocyclic reaction through the isocyanate **285** (Scheme 27). Treatment of the

5-bromoimidazole **281** with *n*-BuLi, followed by the addition of tributyltin chloride gave stannylimidazole, which was then subjected to a Pd-catalyzed cross-coupling reaction<sup>11</sup> with methyl 2-bromobenzoate (**280**) to yield the 5-phenylimidazole **283**. Hydrolysis of the crude **283** with 10% NaOH yielded the carboxylic acid **284**. Compound **284** was treated with DPPA at 50 °C in benzene, and then the solvent was replaced with *o*-dichlorobenzene. The electrocyclic reaction of **285** proceeded smoothly to give imidazo[4,5-*b*]quinoline **286**, which was converted to 4-chloroimidazo[4,5-*c*]quinoline **126** with POCl<sub>3</sub>. Compound **126** was consistent with the former **126** synthesized through the oxime's route (III-1-2). Finally, treatment of conc. NH<sub>4</sub>OH in a sealed tube followed by the reduction of Red-Al provided imiquimod (**127**).<sup>30</sup>

Scheme 27



#### IV. CONCLUSION

As described above, our synthetic strategy was confirmed to be applicable for the construction of a variety of fused hetero-aromatic ring systems including natural products. Based on these results, we are attempting to synthesize a highly substituted carbazole alkaloid by applying the allene-mediated electrocyclic reaction. The development of a synthesis of bioactive fused pyridine ring systems including natural products using a MW-assisted electrocyclic reaction of an aza 6π-electron system is also in progress.

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