The Total Synthesis of Biosynthetically Related Monoterpene Indole Alkaloids

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Abstract: Total syntheses of the biosynthetically–related monoterpene indole alkaloids, (−)–rhazinilam, (−)–rhazinicine, (−)–merscarpine, leuconodine B, melodinine E, and leuconoxine are described. Total synthesis of (−)–rhazinilam was achieved by each of two strategies; 1) regioselective 1,3–dipolar cycloaddition of an optically active münchnone intermediate prepared from α–aspartic acid dimethyl ester; 2) construction of the indolizinone core by a gold–catalyzed double cyclization cascade. The second generation synthetic route was also applied to the first asymmetric total synthesis of (−)–rhazinicine. In addition, the intramolecular gold–catalyzed double cyclization cascade was extended to a novel synthesis of substituted pyrroles, in which gold catalysts behaved as an auto–tandem catalyst, and played a dual role in activating terminal acetylenes both by forming gold acetylides and by σ–coordination. A concise total synthesis of (−)–merscarpine was achieved by an six–pot/nine–step sequence in 21% overall yield from commercially available 2–ethylcyclohexanone. An azepino[3,2–b]indole intermediate was synthesized via d’Angelo’s asymmetric Michael addition, Fischer indole synthesis, and DIBALH–mediated reductive ring–expansion reaction. Finally, divergent total syntheses of leuconodine B, melodinine E, and leuconoxine were achieved. The crucial formation of the key [5.5.6.6]diazafenestrane intermediate was accomplished by oxidative cyclic amidation and regioselective ring–closing metathesis.

1. Introduction

The monoterpene indole alkaloids make up an important family of natural products of rich structural diversity, and a number of compounds in this class possess potent biological activities.1 Their biosynthesis is proposed to proceed via Pictet–Spengler condensation of tryptamine (1) with secologanin (2), followed by formation of the pentacyclic aspidosperma skeleton to generate a pivotal intermediate, vincadifformine (3), which leads into a wide variety of aspidosperma alkaloids and medicinally important vinca alkaloids such as vinblastine and vincristine (Scheme 1).2 On the other hand, a separate branch of the biosynthetic sequence starting from vincadifformine (3) has been proposed to provide a subfamily of aspidosperma alkaloids with an intriguing skeletal diversity. Thus, oxidative rearrangement of aspidospermidine (4) affords leuconolam (5) and rhazinilam (6) both having the [6.9.6.5] ring system.3 Transannular cyclization of leuconolam (5) then provides melodinine E (7) possessing a characteristic aminal–embedded [5.5.6.6]diazafenestrane skeleton.4 Several congeners of different oxidation state such as (−)–leuconoxine (8) (a.k.a. diaza–spiruleonolam) and (−)–leucodolam B (9) (a.k.a. (−)–scholarisin G) are suggested to be biosynthetically derived from melodinine E (7).5 Interestingly, merscarpine (10) having the azepino[3,2–b]indole ring system was also proposed to be derived from melodinine E (7) via skeletal rearrangement with loss of a ketene unit.6

The characteristic, diverse frameworks of this subfamily of natural products biosynthetically derived from the aspidosperma alkaloids have attracted considerable attention from the synthetic community. Tremendous efforts have been directed toward synthesis of these compounds7 as well as attempts to establish a unified synthetic strategy for them8 inspired by the proposed biosynthetic pathways. We too have been intrigued by the highly diverse ring systems and the proposed biosynthetic interrelationship of these monoterpene indole alkaloids, and have initiated a synthetic program for these compounds based on development of new synthetic strategies or tactics dependent on the characteristic structural features of each compound.9–12

Scheme 1. Proposed biosynthetic route to monoterpene indole alkaloids
2. Total Syntheses of (−)-Rhazinilam (6) and (−)-Rhazinicine (11)

2.1 Total Synthesis of (−)-Rhazinilam (6) by 1,3-Dipolar Cycloaddition of a Münchnone Intermediate

Rhazinilam (6) has been isolated from various Apocynaceae species, and originally from Rhaza stricta decaisne. It possesses the biological property of interfering with tubulin polymerization and dynamics. In contrast to more usual antimitotic agents, (−)-rhazinilam (6) demonstrates the activities of both paclitaxel and vincas alkaloids. Because of this, rhazinilam (6) and its congener, rhazinicine (11) have raised expectations as lead compounds for the development of new anti-tumor agents. In addition, its unique structural features, a nine–membered lactam ring fused to its 5,6,7,8-tetrahydroindolinolizine skeleton and a quaternary carbon center, have attracted broad interest to the compound as a synthetic target, and provided a motive to develop novel synthetic methodologies and tactics.

Our first retrosynthetic analysis of (−)-rhazinilam (6) features construction of the tetrahydroindolinolizine core by 1,3-dipolar cycloaddition of a münchnone intermediate (Scheme 2). The 9-membered lactam should then easily be formed under dehydration conditions in the final stage of the synthesis. As components in the 1,3-dipolar cycloaddition we planned to use arylacetylene 13 and the fully elaborated optically active münchnone 14, which should be generated on treatment of N-formyl pipecolinic acid derivative 15 with acetic anhydride. Compound 15 having a quaternary stereogenic center, should be readily available from the known amino ester 16. Finally, a six-step synthesis of 16 from d-aspartic acid dimethyl ester was established using Rapoport and co-workers during their synthetic studies on vindoline.

Scheme 2. Retrosynthesis of (−)-rhazinilam (6) using 1,3-dipolar cycloaddition of a münchnone intermediate.

It was reported that the regioselectivity of the [3+2] cycloaddition reactions of münchnones generally depends on their substitution pattern. Therefore, we initially investigated this regiochemistry using a simple N-formyl pipecolinic acid (17) and arylacetylenes 13a−13c (Scheme 3). When N-formyl pipecolinic acid (17) was heated at reflux in acetic anhydride in the presence of phenylacetylene (13a) or a substrate (13b) having a methoxycarbonyl group, the expected tetrahydroindolinolizine product 18a or 18b was not obtained at all. On the other hand, reaction of nitro-substituted arylacetylenes 13c proceeded smoothly to give the product of cycloaddition followed by decarboxylation as a single compound in good yield.

Having obtained this promising result from our model studies, synthetic studies on (−)-rhazinilam (6) were initiated by preparation of the fully–functionalized münchnone precursor, intermediate 15 (Scheme 4). Based on Rapoport’s procedure, methyl pipecolate 16 was synthesized from d-aspartic acid dimethyl ester using a five-step sequence. Next, compound 16 was converted to the N-formyl pipecolinic acid 15 by N-formylation followed by chemoselective hydrolysis of the diester. The crucial [3+2] cycloaddition proceeded when the functionalized pipecolinic acid 15 and (2–nitrophenyl)acetylene (18c) were heated at reflux in acetic anhydride to furnish 1-aryl tetrahydroindolinolizine 19 as the sole product in 94% yield. After conversion of this ester to aldehyde 20, the side chain was elongated using the Horner–Wadsworth–Emmons reaction. Reduction of the olefin and nitro group then gave amino ester 21. Finally, basic hydrolysis of the ester and subsequent lactamization completed the total synthesis of (−)-rhazinilam (6). This concise total synthesis from the known compound 16 in an overall yield of 21% requires 9 steps (calculated from d-aspartic acid dimethyl ester, (−)-rhazinilam (6) was synthesized in 14 steps with an overall yield of 7.1%).
cycloaddition. Thus, only seven further steps were required to complete the synthesis of the target compound. However, preparation of the precursor of highly functionalized münchnone intermediate 15 was inefficient and required a lengthy linear sequence. Therefore, we reinvestigated synthesis of rhazinilam (6) aiming to develop a more practical and efficient route.

Our second generation retrosynthetic analysis of rhazinilam (6) is depicted in Scheme 5. The nine-membered lactam ring was to be formed at the final stage of the synthesis by an intramolecular aromatic amidation reaction. For construction of the indolizinone skeleton, we decided to devise a novel double cyclization of a linear ynamide 23. A working hypothesis for this reaction is shown in Scheme 6. We considered that intramolecular nucleophilic addition of nitrogen to the acetylene in 6-exo-dig mode should proceed on activation of the acetylene with a π-phlic metal catalyst. Then, cyclization of the resultant enamides 28 to the terminal acetal moiety and subsequent aromatization should provide indolizinone 29. The fully elaborated ynamide 23, the substrate for the double cyclization, should be readily prepared by assembling the three segments 24–26 using amide formation and Sonogashira coupling.

Scheme 5. Our second generation retrosynthetic analysis of (−)-rhazinilam (6) and (−)-rhazinicine (11).

Scheme 6. Working hypothesis for 5-indolizinone formation.

First, we examined a model reaction using a simple ynamide 27a (Scheme 7). Treatment of this with π-phlic metal catalysts such as AuCl, AuCl₃, Au(PPh₃)Cl, or a combination of AuCl with AgOTf in 1,2-dichloroethane at 80 °C gave neither enamide intermediate nor indolizinone 29a. On the other hand, a combination of Au(PPh₃)Cl and AgOTf promoted the expected sequential processes all the way through to the bicyclic product 29a, albeit in low yield. Extensive optimizations revealed that pre-formed Au(PPh₃)NTf₂ was quite effective as catalyst, and 29a was obtained in 69% yield on heating a mixture of this (10 mol%) and 27a in dioxane (0.1 M).

Scheme 7. Optimization of reaction conditions using a model substrate.

Having established the optimal conditions for construction of the indolizine skeleton, we started synthetic studies on (−)-rhazinilam (6) by preparing the fully-functionalized ynamide 23 (Scheme 8). Ketoester 31 was synthesized in optically pure form using d’Angelo’s diastereoselective Michael reaction. Compound 31 was then converted in a three-step sequence to epoxystereone 32, and this was condensed with semicarbazide. A modified Eschenmoser–Tanabe type fragmentation was achieved by oxidative treatment giving the aldehyde containing a terminal acetylene. Finally, this aldehyde was oxidized to carboxylic acid 33, which was condensed with aminocetaldehyde dimethylacetal, after which Sonogashira coupling with 2-bromiodobenzene furnished the key ynamide 23.

Scheme 8. Preparation of the fully–elaborated ynamide 23.

With the fully–functionalized ynamide 23 in hand, we examined the crucial double cyclization cascade. Disappointingly however, the first trial under the original optimized conditions provided the desired indolizinone 22 in only 28% yield. Hypothesizing that the low yield may be due to decomposition of the acetal moiety and subsequent reaction of the triple bond by gold–catalyzed methanalysis, we synthesized disopropyl acetal 34 and tested it in the cascade reaction (Scheme 9). In this case, the expected reaction proceeded best under microwave irradiation (one minute x 40 intervals) in the presence of catalytic KHSO₃ in 2-propanol and dioxane to...
furnish the desired indolizinone 22 in 65% yield. The highly reactive N-acylpyrrole was reduced stepwise to give 35. Aryl bromide 35 was then converted to aniline 36 by copper-mediated amination reaction via the azide. Finally basic hydrolysis of the ester, followed by lactamization completed the total synthesis of (−)-rhazinilam (6).

The key indolizinone intermediate 22 obtained from the double cyclization cascade was then converted to (−)-rhazinicine (11) with the highly reactive N-acylpyrrole moiety untouched (Scheme 9). An attempt to introduce an amino group using the copper-catalyzed amination reaction with sodium azide resulted in decomposition of 22. Therefore, we developed a different endgame sequence. Methyl ester 22 was treated with TMSI to give the corresponding carboxylic acid, which was condensed with ammonia to give amide 37. Finally, the nine-membered lactam ring was constructed by copper-mediated intramolecular amidation to furnish (−)-rhazinicine (11).

In summary, as described above, we have achieved a total synthesis (−)-rhazinilam (6) and the first asymmetric total synthesis of (−)-rhazinicine (11) by development of a gold-catalyzed double cyclization cascade to construct the fully functionalized indolizinone intermediate. It is notable that these total syntheses did not require the use of protecting groups.

2.3 Application of Gold-catalyzed Sequential Double Cyclization Cascade to Multi-substituted Pyrrole Synthesis: An Auto-tandem Catalysis

The pyrrole ring is a fundamental nitrogen–heterocycle, and as such development of synthetic methodology for pyroles continues (Scheme 9). An attempt to introduce an amino group using the copper-catalyzed pyrrole amination reaction with sodium azide resulted in decomposition of 22. Therefore, we developed a different endgame sequence. Methyl ester 22 was treated with TMSI to give the corresponding carboxylic acid, which was condensed with ammonia to give amide 37. Finally, the nine-membered lactam ring was constructed by copper-mediated intramolecular amidation to furnish (−)-rhazinicine (11).

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To obtain mechanistic information control reactions using modified substrates 43 and 45 were investigated (Scheme 12). Amide 43 without an acetal moiety provided a trace amount...
of enamide 44, with recovery of the starting 43 in 93% yield, suggesting that the initial step is not nucleophilic addition of a nitrogen atom to the activated acetylene, as in the intramolecular reaction. On the other hand, clean formation of acetylene adduct 46 was observed when using protected amide 45, indicating involvement of a gold acetylide \(^{29}\) generated from the terminal acetylene and the cationic gold catalyst, which can then add to an oxonium ion.

A possible reaction mechanism based on the control reactions and the unexpected regiochemistry is shown in Scheme 13.\(^{30}\) This reaction might be initiated by addition of gold acetylide \(^{47}\) to oxonium ion \(^{48}\). The resultant adduct \(^{49}\) should undergo \(^5\)\(^\text{endo-dig}\) cyclization on activation of the acetylene moiety by the π-philic gold catalyst. Subsequent protonolysis of the carbon–gold bond and aromatization should provide pyrrole product \(^{42}\). Overall, the reaction involves auto–tandem catalysis.\(^{31}\) Thus, the one gold catalyst catalyzes two different catalytic cycles A and B by differential activation of a terminal acetylene by σ-coordination and π-coordination, respectively.

This reaction has a broad substrate scope and various functional groups are compatible with these reaction conditions (Scheme 14). Arylalkynes bearing electron-donating substituents such as methoxy, methyl, and protected amino groups, or a halogen, such as a bromo group at the para position of the benzene ring, served as good substrates, although arylalkynes bearing electron-withdrawing groups exhibited lower reactivity. It is notable that an alkyl-substituted alkyne can be used in the reaction.

Furthermore, this reaction was applicable to the construction of multisubstituted pyrroles (Scheme 15). Thus, reaction of acetals \(^{53}, \, ^{54}, \, ^{55}\), which were derived from (−)-alanine, and glycine, proceeded under slightly modified conditions to give the corresponding 1,2,5-, 1,2,3,5-, and 1,2,4-substituted pyrroles \(^{56}, \, ^{57}, \, ^{58}\), respectively.

3. Total Synthesis of (−)-Mersicarpine (10)\(^{11}\)

Mersicarpine (10), isolated \(Kopsia fruticosa\) and \(Kopsia arborea\) by Kam and co-workers in 2004,\(^{32}\) possesses a unique structure, a seven-membered cyclic imine fused with δ-lactam...
and indoline rings. These characteristic structural features have attracted broad interest to this synthetic target and a number of total syntheses and synthetic studies have so far been reported, including Kerr’s first total synthesis of (−)-10\(^7\) and Fukuyama’s first total synthesis of (−)-10.\(^7\) Since we published a review article on total syntheses of this compound in the previous issue of this journal, we will briefly describe our synthesis in this chapter.

After preliminary investigation of several synthetic routes, we finally examined one based on the retrosynthetic analysis shown in Scheme 16. Fukuyama’s autoxidation–reduction sequence\(^7\) (Scheme 17) and an analogous reaction by Hester suggested to us the selection of azepinoindole lactam as a precursor to mersicarpine (10). For the construction of the azepin ring of tetracyclic indole 59, we decided to apply the DIBALH-mediated reductive ring-expansion reaction of ketoximes, which we have recently studied in detail\(^7\) (Scheme 18). The oxime 60 should be readily prepared from tetrahydrocarbazole derivative via oxidation to ketone (X=O) and condensation with hydroxylamine. Tetrahydrocarbazole derivative 61 would be accessible from phenylhydrazine and optically active cyclohexanone 63 by Fischer indole synthesis.

First, we examined the applicability of the DIBALH-mediated reductive ring-expansion reaction of a cyclic ketoxime (Scheme 19) to constructing azepinoindoles. This was found to work with oxime to give the desired azepinoindole 66 in good yield after protection as an amide due to the instability of amine 65 to air (Scheme 19).

Having proved the feasibility of applying the reductive ring expansion reaction to the construction of azepinoindoles, we then synthesized the fully elaborated oxime and tested it as a substrate. First, cyclohexanone 63 was prepared in optically pure form by asymmetric Michael addition according to the d’Angelo protocol\(^22\) (Scheme 20). Fischer indole synthesis of 63 and phenylhydrazine was best effected with two equivalents of phenylhydrazine and 1.9 equivalents of methanesulfonic acid in refluxing methanol to afford the desired tricyclic indole 61 in 84\% yield. Then regioselective oxidation with DDQ and condensation of the resultant ketone with hydroxylamine furnished oxime 67. The crucial ring expansion reaction of oxime 67 proceeded as expected to provide the desired azepinoindole, which was isolated in its Cbz-protected form in 74\% yield after the reaction mixture was directly subjected to Schotten-Baumann conditions. Next, a one-pot conversion of alcohol to lactam was executed with TPAP and NMO. Removal of the Cbz group, followed by autoxidation of the resultant

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**Scheme 16.** Retrosynthetic analysis of (−)-mersicarpine.

**Scheme 17.** Fukuyama’s synthesis of (−)-mersicarpine.

**Scheme 18.** DIBALH-mediated reductive ring-expansion.

**Scheme 19.** Model studies on construction of azepinoindole skeleton.

**Scheme 20.** Total synthesis of (−)-mersicarpine (10).
azeponindole 59 and reductive treatment with dimethyl sulfide completed the total synthesis of (-) 10. The overall yield of this concise nine-step/six-pot total synthesis of (-) -mersicarpine (10) from ketoester 63 was 21%.

4. Divergent Total Syntheses of Leuconoxine (8), Leuconodine B (9), and Melodinine E (7)

Among those monoterpene indole alkaloid family members which have been proposed to be biosynthesized from (+)-vincadifformine, several compounds possess a [5.5.6]diazafenestrane skeleton containing within it an aminal, for example leuconoxine (8), 26 leuconodine B (9), 27 and melodinine E (7). 36 We have established a divergent route to these compounds utilizing a newly developed oxidative cyclic aminal formation and a diastereoselective ring-closing metathesis. 12

We selected leuconodine B (9) as a precursor to leuconoxine (8) and melodinine E (7) (Scheme 21). Deoxygenation and dehydration of leuconodine B (9) should give leuconoxine (8) and melodinine E (7), respectively. We planned to construct the [5.5.6]diazafenestrane structure by oxidative cyclic aminal formation using indole 3 acetamide 71 and subsequent diastereoselective ring-closing olefin metathesis using triene 70. The gem-divinyl group attached to the indole C2 position of compound 71 would be formed by an intramolecular Mizoroki-Heck reaction of N'-acylindole derivative 72, which should be available from 2-iodoindole 3 acetate 73 and carboxylic acid 74.

Disappointingly, the expected oxidative cyclic aminal formation did not proceed on treatment of 71 with various oxidants (Scheme 23). On the other hand, DMDO oxidation of compound 80 lacking the lactam ring did occur at the indole C2–C3 bond to afford hydroxyindolenine 81.
The next task was to establish conditions for the cyclic aminal formation. Initial trials using treatment of hydroxyindolenine 81 with Lewis acids such as BF$_3$·Et$_2$O or Sc(OTf)$_3$ gave the unexpected 3,3-disubstituted oxindole 82 (Scheme 24). An analogous reaction had also been reported by Movassaghi and co-workers. Given the unsuccessful results using Lewis acids, we then examined activation of the amide moiety as its TMS imidate. Interestingly, significant acceleration of cyclic aminal formation was observed upon treatment of hydroxyindolenine 81 with TMSOTf and 2,6-lutidine which afforded the desired aminal product 83 in 93% yield without formation of rearrangement side-product. The facile cyclization implies formation of a silyl imidate intermediate enhancing the nucleophilicity of the amide moiety. Before construction of the [5.5.6.6]diazafenestrane skeleton, the δ-lactam ring was formed by basic treatment of aminal 83 with t-BuOK with loss of the TMS group. The crucial formation of the [5.5.6.6]diazafenestrane framework was effected by ring-closing metathesis of triene 70 with Hoveyda–Grubbs 2nd generation catalyst to furnish the pentacyclic [5.5.6.6]diazafenestrane compound 84 as a single isomer. Finally, a total synthesis of leuconodine B (9) was completed by hydrogenation of the two olefinic bonds.

Having established a total synthesis of leuconodine B (9), we then converted this to leuconoxine (8) and melodidine E (7) (Scheme 25). A dehydroxylation reaction of the methyl xanthate derivative of leuconodine B (9) under standard Barton–McCombie deoxygenation conditions furnished leuconoxine (8). Furthermore, an elimination reaction of xanthate 85 proceeded on treatment with DBU under microwave irradiation to afford melodidine E (7).

5. Conclusion

The structurally diverse monoterpenoid indole alkaloids provided us with good opportunities to develop several new synthetic methodologies and tactics dependent on each individual compounds characteristic structural motifs. For the synthesis of (−)-rhazinilam (6) and (−)-rhazinic (11), we focused on facile construction of the fully elaborated quinolizidine core and successfully developed two strategies. One uses regioselective 1,3-dipolar cycloaddition of an optically active minichrome intermediate. The latter utilizes a gold−catalyzed double cyclization cascade of a fully functionalized ynamide derivative. The latter chemistry was extended to the synthesis of substituted pyrroles by application to the intermolecular process, in which the gold catalyst played two distinct processes as an auto–tandem catalyst. By accomplishing the total synthesis of (−)-merscarpine (10) containing the azepino[3,2-b]indole ring system, we have effectively demonstrated the utility of the DIBALH-mediated reductive ring expansion reaction of ketoximes. This strategy allowed us to access 3-aminoindole derivatives, which are not easily synthesized by conventional methodologies. During synthetic studies on the series of compounds leuconoxine (8), leuconodine B (9), and melodidine E (7) possessing the intriguing [5.5.6.6]diazafenestrane skeleton containing an aminal carbon, we faced difficulty forming this group due to an unexpected rearrangement of the side-chain. This was overcome by activation of an amide as the corresponding silyl imidate. Because of their versatility, a number of the methodologies developed during the course of these synthetic studies on the aspidosperma subfamily of monoterpenoid indole alkaloids should find convenient use in the synthesis not only of related monoterpenoid indole alkaloids, but also other nitrogen−containing heterocycles.

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PROFILE

Hidetoshi Tokuyama was born in Yokohama in 1967. He received his Ph.D. in 1994 from the Tokyo Institute of Technology under the direction of Professor Ei-ichi Nakamura. He spent one year (1994-1995) at the University of Pennsylvania as a JSPS postdoctoral fellow with Professor Amos B. Smith, III. He joined the group of Professor Tohru Fukuyama at the University of Tokyo in 1995 and was appointed associate professor in 2003. In 2006, he moved to Tohoku University, where he is currently a professor. His research interests are the development of synthetic methodologies and the total synthesis of natural products. His work has been honored with the Pharmaceutical Society Japan Award for Young Scientist (2003), Young Scientist's Prize: The Commendation for Science and Technology by the MEXT, Japan (2007), Daiichi-Sankyo Award for Medicinal Chemistry 2015 from the Society of Synthetic Organic Chemistry, Japan (2014), The Pharmaceutical Society of Japan Award for Divisional Scientific Promotions (2014), and ISHC Alan. R. Katritzky Junior Award in Heterocyclic Chemistry (2015).