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, (–)-mersicarpine, 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 D-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 π -coordination. A concise total synthesis of (–)-mersicarpine 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 amination formation 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 amination-embedded [5.5.6.6]diazafenestrane skeleton.⁴ Several congeners of differ-

ent oxidation state such as (–)-leuconoxine (**8**) (a.k.a. diaza-spiroleuconolam) and (–)-leuconodine B (**9**) (a.k.a. (–)-scholarisine G) are suggested to be biosynthetically derived from melodinine E (**7**).⁵ Interestingly, mersicarpine (**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 Intermediate⁹

Rhazinilam (6) has been isolated from various *Apocynaceae* species,¹³ and originally from *Rhazya stricta decaisne*. It possesses the biological property of interfering with tubulin polymerization and dynamics.¹⁴ In contrast to more usual antimitotic agents, (–)-rhazinilam (6) demonstrates the activities of both paclitaxel and vinca alkaloids. Because of this, rhazinilam (6) and its congener, rhazinicine (11)¹⁵ 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-tetrahydroindolizine 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.^{7a-j}

Our first retrosynthetic analysis of (–)-rhazinilam (6) features construction of the tetrahydroindolizine core by 1,3-dipolar cycloaddition of a münchnone intermediate¹⁶ (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 by Rapoport and co-workers during their synthetic studies on vindoline.¹⁷

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.¹⁶ Therefore, we initially investigated this regiochemistry using a simple *N*-formyl pipecolinic acid (17) and arylacetylenes¹⁸ 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 tetrahydroindolizine 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

Scheme 3. Model reaction of [3+2] cycloaddition of münchnone.

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,¹⁶ 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 (13c) were heated at reflux in acetic anhydride to furnish 1-aryl tetrahydroindolizine 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%).

Scheme 4. Total synthesis of (–)-rhazinilam (6).

2.2 Total Synthesis of (–)-Rhazinilam (6) and (–)-Rhazinicine (11) by Gold-catalyzed Sequential Double Cyclization Cascade¹⁰

An advantage of the first generation total synthesis of (–)-rhazinilam (*vide supra*) was its high efficiency after the key

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 -philic metal catalyst.¹⁹ Then, cyclization of the resultant enamide **28** to the terminal acetal moiety and subsequent aromatization should provide indolizinone **29**.²⁰ 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 -philic 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)NTf₂²¹ 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 indolizinone 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.²² Compound **31** was then converted in a three-step sequence to epoxyketone **32**, and this was condensed with semicarbazide. A modified Eschenmoser–Tanabe-type fragmentation²³ 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 aminoacetaldehyde 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 methanolysis, we synthesized diisopropyl 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 KHSO₄ in 2-propanol and dioxane to

Scheme 9. The crucial gold-catalyzed double cyclization cascade and endgame sequences for (–)-rhazinilam (**6**) and (–)-rhazinicine (**11**).

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.²⁴ 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 amidation²⁵ 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 Catalysis²⁶

The pyrrole ring is a fundamental nitrogen-heterocycle, and as such development of synthetic methodology for pyrroles continues to be an important topic in synthetic organic chemistry. Having established a novel construction of the indolizinone skeleton (*vide supra*), we decided to extend this chemistry to the synthesis of various substituted pyrroles. Thus, based on the reaction mechanism proposed for the intramolecular double cyclization cascade (Scheme 6), we considered that intermolecular reaction of acetals **38** with terminal acetylenes **39** should give 3-substituted *N*-acylpyrroles **41** (Scheme 10).

With this idea in mind, we subjected acetal **38a** and phenylacetylene **39a** to the standard conditions established for the

Scheme 10. Working hypothesis for pyrrole synthesis.

intramolecular reaction (Scheme 11). While a low yield of pyrrole product was obtained, this was not the expected 3-phenylpyrrole **41a**, but rather 2-phenylpyrrole **42a**. Nevertheless, the reaction conditions were optimized to improve the yield. After extensive experimentation, we eventually established two sets of reaction conditions; Conditions A: heating at 140 °C in xylene using dimethyl acetal **38a**, IPrAuCl²⁷ (3 mol%), and AgOTf (3 mol%); Conditions B: heating at 110 °C in toluene using diisopropyl acetal **38b**, RuPhosAuCl (10 mol%), and AgOTf (10 mol%).

Scheme 11. First attempt and optimal conditions for intermolecular reaction.

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

Scheme 13. Plausible mechanism for auto-tandem gold-catalysis in the cascade reaction.

Scheme 12. Control reactions using modified substrates.

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 acetylide²⁹ 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-*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**, and **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

Scheme 14. Substrate scope for alkynes.

Scheme 15. Syntheses of tri- and tetrasubstituted pyrroles.

pyrroles **56**, **57**, and **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 ($\pm$)-**10**^{7k} and Fukuyama's first total synthesis of (–)-**10**.⁷ⁿ 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.³³

After preliminary investigation of several synthetic routes, we finally examined one based on the retrosynthetic analysis shown in Scheme 16. Fukuyama's autoxidation–reduction sequence⁷ⁿ (Scheme 17) and an analogous reaction by Hester³⁴ suggested to us the selection of azepinoindole lactam **59** 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 detail³⁵ (Scheme 18). The oxime **60** should be readily prepared from tetrahydrocarbazole derivative **61** (X=H₂) via oxidation to ketone **61'** (X=O) and condensation with hydroxylamine. Tetrahydrocarbazole derivative **61** would be accessible from phenylhydrazine (**62**) and optically active cyclohexanone **63** by

Scheme 16. Retrosynthetic analysis of (–)-mersicarpine.

Scheme 17. Fukuyama's synthesis of (–)-mersicarpine.

Scheme 18. DIBALH-mediated reductive ring-expansion.

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 **64** 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).

Scheme 19. Model studies on construction of azepinoindole skeleton.

Having proved the feasibility of applying the reductive ring expansion reaction to the construction of azepinoindoles, we then synthesized the fully-elaborated oxime **67** and tested it as a substrate. First, cyclohexanone **63** was prepared in optically pure form by asymmetric Michael addition according to the d'Angelo protocol²² (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 **68** in 74% yield after the reaction mixture was directly subjected to Schotten-Baumann conditions. Next, a one-pot conversion of alcohol **68** to lactam **69** was executed with TPAP and NMO. Removal of the Cbz group, followed by autoxidation of the resultant

Scheme 20. Total synthesis of (–)-mersicarpine (**10**).

azepinoindole **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**)¹²

Among those monoterpene indole alkaloid family members which have been proposed to be biosynthesized from (+)-vincadifformine, several compounds possess a [5.5.6.6]diazafenestrane skeleton containing within it an aminal, for example leuconoxine (**8**),³⁶ leuconodine B (**9**),³⁷ and melodinine E (**7**).³⁸ 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 [5.5.6.6]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**.

Scheme 21. Retrosynthetic analysis.

Preparation of *N*-acylindole derivative **72** commenced with Baeyer–Villiger oxidation of 1,4-cyclohexanedione **75**³⁹ to give ketolactone **76**, which was ring-opened by methanolysis to give ketoester **77** after protection as a TBS ether (Scheme 22). Wittig reaction of this ketoester afforded the desired ethylidene product as an *E/Z* mixture in 39% yield with 37% recovery of **77**. After four cycles the product was obtained in 57% total yield. Basic hydrolysis then provided carboxylic acid **74**. While the next *N*-acylation of indole **73** was not an easy task, we found treatment of **74** with Boc₂O followed by addition of **73** in the presence of DMAP and Et₃N was effective and gave the desired *N*-acylindole **72** in good yield. The

intramolecular Mizoroki–Heck reaction of **72** proceeded smoothly in the presence of Pd₂(dba)₃·CHCl₃, P(*o*-tol)₃, and 1,2,2,6,6-pentamethylpiperidine (PMP)⁴⁰ to afford the desired lactam **78**. Next, the *gem*-divinyl group was constructed by removal of the TBS group and subsequent dehydration using the Grieco–Nishizawa protocol.⁴¹ Finally, methyl ester **79** was converted to the corresponding *N*-allylamide **71**.

Scheme 22. Preparation and intramolecular Heck reaction of *N*-acylindole derivative **72**.

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**.

Scheme 23. Attempted oxidative cyclization of lactam **71**, and preparation of 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 $\text{BF}_3 \cdot \text{Et}_2\text{O}$ or $\text{Sc}(\text{OTf})_3$ gave the unexpected 3,3-disubstituted oxindole **82** (Scheme 24). An analogous reaction had also been reported by Movassaghi and co-workers.⁴² 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.⁴³ 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.

Scheme 24. Total synthesis of leuconodine B (**9**).

Having established a total synthesis of leuconodine B (**9**), we then converted this to leuconoxine (**8**) and melodinine E (**7**) (Scheme 25). A dehydroxylation reaction of the methyl xanthate derivative of leuconodine B (**9**) under standard Barton–McCombie deoxygenation⁴⁴ conditions furnished leuconoxine (**8**). Furthermore, an elimination reaction of xanthate **85** proceeded on treatment with DBU under microwave irradiation to afford melodinine E (**7**).

5. Conclusion

The structurally diverse monoterpene indole alkaloids provided us with good opportunities to develop several new synthetic methodologies and tactics dependent on each individual

Scheme 25. Total syntheses of leuconoxine (**8**) and melodinine E (**7**).

compounds characteristic structural motifs. For the synthesis of (–)-rhazinilam (**6**) and (–)-rhazinicine (**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 münchnone intermediate. The other 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 (–)-mersicarpine (**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 melodinine 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 monoterpene indole alkaloids should find convenient use in the synthesis not only of related monoterpene indole alkaloids, but also other nitrogen-containing heterocycles.

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References

- (a) Takayama, H.; Sakai, S.-I. In *The Alkaloids: Chemistry and Biology*; Cordell, G. A., Ed.; Academic Press: New York, 1998; Vol. 50, p 415. (b) Kam, T.-S.; Lim, K.-H.; In *The Alkaloids: Chemistry and Biology*; Cordell, G. A., Ed.; Academic Press: The Netherlands, 2008; Vol. 66, p 1. (c) Ishikura, M.; Yamada, K.; Abe, T. *Nat. Prod. Rep.* **2010**, *27*, 1630.
- Szabó, L. F. *ARKIVOC*, **2008**, *3*, 167.
- (a) Croquelois, G.; Kunesche, N.; Posson, J. *Tetrahedron Lett.* **1974**, *15*, 4427. (b) Goh, S. H.; Ali, A. R. M. *Tetrahedron Lett.* **1986**, *27*, 2501.
- Hugel, P. G.; Lévy, L.; Le Man, J. *Tetrahedron Lett.* **1974**, *15*, 3109.
- Gan, C.-Y.; Low, Y.-Y.; Thomas, N. F.; Kam, T.-S. *J. Nat. Prod.* **2013**, *76*, 957.
- Kam, T.-S.; Subramaniam, G.; Lim, K.-H.; Choo, Y.-M. *Tetrahedron Lett.* **2004**, *45*, 5995.
- For syntheses of (±)-rhazinilam, see: (a) Ratcliffe, A. H.; Smith, G. F.; Smith, G. N. *Tetrahedron Lett.* **1973**, *14*, 5179. (b) Sames, D.; Johnson, J. A. *J. Am. Chem. Soc.* **2000**, *122*, 6321. (c) Magnus, P.; Rainey, T. *Tetrahedron* **2001**, *57*, 8647. (d) Banwell, M. G.; Edwards, A. J.; Jolliffe, K. A.; Smith, J. A.; Hamel, E.; Verdier-Pinard, P. *Org. Biomol. Chem.* **2003**, *1*, 296. (e) Bowie, Jr. A. L.; Hughes, C. C.; Trauner D. *Org. Lett.* **2005**, *7*, 5207. For syntheses of (–)-rhazinilam, see: (f) Liu, Z.; Wasmuth, A. S.; Nelson, S. G. *J. Am. Chem. Soc.* **2006**, *128*, 10352. (g) Johnson, J. A.; Li, N.; Sames, D. *J. Am. Chem. Soc.* **2002**, *124*, 6900. (h) Banwell, M. G.; Beck, D. A. S.; Willis, A. C. *ARKIVOC* **2006**, 163. (i) Gu, Z.; Zakarian, A. *Org. Lett.* **2010**, *12*, 4224. (j) Gualtierotti, J.-B.; Pasche, D.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2014**, *53*, 9926. For syntheses of (±)-mersicarpine, see: (k) Magolan, J.; Carson, B. A.; Kerr, M. A. *Org. Lett.* **2008**, *10*, 1437. (l) Biechy, A.; Zard, S. Z. *Org. Lett.* **2009**, *11*, 2800. (m) Zhong, X.; Li, Y.; Han, F.-S. *Chem. Eur. J.* **2012**, *18*, 9784. For syntheses of (–)-mersicarpine, see: (n) Nakajima, R.; Ogino, T.; Yokoshima, S.; Fukuyama, T. *J. Am. Chem. Soc.* **2010**, *132*, 1236. For the total syntheses of (–)-leuconoxine, see: (o) Higuchi, K.; Suzuki, S.; Ueda, R.; Oshima, N.; Kobayashi, E.; Tayu, M.; Kawasaki, T. *Org. Lett.* **2015**, *17*, 154. (p) Pfaffenbach, M.; Gaich, T. *Chem. Eur. J.* **2015**, *21*, 6355. For the total syntheses of (–)-leuconoxine, see: Izgu, E. C.; Hoye, T. R. *Chem. Sci.* **2013**, *4*, 2262.
- (a) Xu, Z.; Wang, Q.; Zhu, J. *J. Am. Chem. Soc.* **2013**, *135*, 19127. (b) Xu, Z.; Wang, Q.; Zhu, J. *J. Am. Chem. Soc.* **2015**, *137*, 6712. (c) Yang, Y.; Bai, Y.; Sun, S.; Dai, M. *Org. Lett.* **2014**, *16*, 6216. (d) Li, Z.; Geng, Q.; Lv, Z.; Pritchett, B. P.; Baba, K.; Numajiri, Y.; Stoltz, B. M.; Liang, G. *Org. Chem. Front.* **2015**, *2*, 236.
- Sugimoto, K.; Miyakawa, Y.; Tokuyama, H. *Tetrahedron* **2015**, *71*, 3619.
- Sugimoto, K.; Toyoshima, K.; Nonaka, S.; Kotaki, K.; Ueda, H.; Tokuyama, H. *Angew. Chem. Int. Ed.* **2013**, *52*, 7168.
- (a) Iwama, Y.; Okano, K.; Sugimoto, K.; Tokuyama, H. *Org. Lett.* **2012**, *14*, 2320. (b) Iwama, Y.; Okano, K.; Sugimoto, K.; Tokuyama, H. *Chem. Eur. J.* **2013**, *19*, 9325.
- Umehara, A.; Ueda, H.; Tokuyama, H. *Org. Lett.* **2014**, *16*, 2526.
- (a) Linde, H. H. A. *Helv. Chim. Acta* **1965**, *48*, 1822. (b) Banerji, A.; Majumder, P. L.; Chatterjee, A. G. *Phytochemistry* **1970**, *9*, 1491. (c) Thoison, O.; Guénard, D.; Sévenet, T.; Kan-Fan, C.; Quirion, J.-C.; Husson, H.-P.; Deverre, J.-R.; Chan, K. C.; Potier, P. C. R. *Acad. Sci. Paris II* **1987**, *304*, 157.
- (a) Alazard, J.-P.; Millet-Paullusson, C.; Boyé, O.; Guénard, D.; Chiaroni, A.; Riche, C.; Thal, C. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 725. (b) David, B.; Sévenet, T.; Thoison, O.; Awang, K.; Païs, M.; Wright, M.; Guénard, D. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2155. (c) Baudoin, O.; Claveau, F.; Thoret, S.; Herrbach, A.; Guénard, D.; Guéritte, F. *Bioorg. Med. Chem.* **2002**, *10*, 3395.
- (a) Gerasimenko, I.; Sheludko, Y.; Stöckigt, J. *J. Nat. Prod.* **2001**, *64*, 114. (b) Kam, T. S.; Subramaniam, G.; Chen, W. *Phytochemistry* **1999**, *51*, 159.
- Huisgen, R.; Gotthardt, H.; Bayer, H. O.; Schafer, F. C. *Chem. Ber.* **1970**, *103*, 2611. For the synthetic application of 1,3-dipolar cycloadditions, see: *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; John Wiley & Sons: New York, 2002.
- Feldman, P. L.; Rapoport, H. *J. Org. Chem.* **1986**, *51*, 3882.
- (a) Hershenson, F. M. *J. Org. Chem.* **1972**, *37*, 3111. (b) Hershenson, F. M. *J. Org. Chem.* **1975**, *40*, 740.
- Reviews on Au-catalyzed reactions, see: (a) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (b) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395. (c) Hashmi, A. S. K. *Angew. Chem. Int. Ed.* **2010**, *49*, 5232.
- For related pyrrole synthesis, see: (a) Gorin, D. J.; Davis, N. R.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 11261. (b) Egi, M.; Azechi, K.; Akai, S. *Org. Lett.* **2009**, *11*, 5002. (c) Saito, A.; Konishi, T.; Hanzawa, Y. *Org. Lett.* **2010**, *12*, 372.
- Mézailles, N.; Ricard, L.; Gagosz, F. *Org. Lett.* **2005**, *7*, 4133.
- d'Angelo, J.; Desmaële, D.; Dumas, F.; Guingant, A. *Tetrahedron: Asymmetry* **1992**, *3*, 459.
- Macalpine, G. A.; Warkentin, J. *Can. J. Chem.* **1978**, *56*, 308.
- Markiewicz, J. T.; Wiest, O.; Helquist, P. *J. Org. Chem.* **2010**, *75*, 4887.
- Phillips, D. P.; Zhu, X.-F.; Lau, T. L.; He, X.; Yang, K.; Liu, H. *Tetrahedron Lett.* **2009**, *50*, 7293.
- Ueda, H.; Yamaguchi, M.; Kameya, H.; Sugimoto, K.; Tokuyama, H. *Org. Lett.*, **2014**, *16*, 4948.
- Fructos, M. R.; Belderrain, T. R.; de Frémont, P.; Scott, N. M.; Nolan, S. P.; Diaz-Requejo, M. M.; Pérez, P. J. *Angew. Chem. Int. Ed.* **2005**, *44*, 5284.
- Wang, T.; Zhang, J. *Chem. Eur. J.* **2011**, *17*, 86.
- (a) Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* **2003**, *125*, 9584. (b) Bucher, J.; Thomas, W.; Nalivela, K. S.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. *Angew. Chem. Int. Ed.* **2014**, *53*, 3854.
- For the similar addition-cyclization reaction catalyzed by gold catalyst, see: (a) Yan, B.; Liu, Y. *Org. Lett.* **2007**, *9*, 4323. (b) Suzuki, Y.; Naoe, S.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2012**, *14*, 326. (c) Liu, J.; Ding, D.; Sun, J.; Ji, Y.; Dong, J. *Org. Lett.* **2013**, *15*, 2884.
- (a) Gleason, J.; Ajamain, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 3754. (b) Chang, S. *Chem. Soc. Rev.* **2004**, *33*, 302. (c) Baker, R.; Bazan, G. *Chem. Rev.* **2005**, *105*, 1001.
- Kam, T.-S.; Subramaniam, G.; Lim, K.-H.; Choo, Y.-M. *Tetrahedron Lett.* **2004**, *45*, 5995.
- Iwama, Y.; Okano, K.; Tokuyama, H. *J. Synth. Org. Chem., Jpn.* **2013**, *71*, 926.
- Hester Jr., J. B. *J. Org. Chem.* **1967**, *32*, 3804.
- (a) Cho, H.; Iwama, Y.; Sugimoto, K.; Kwon, E.; Tokuyama, H. *Heterocycles* **2009**, *78*, 1183. (b) Cho, H.; Iwama, Y.; Sugimoto, K.; Mori, S.; Tokuyama, H. *J. Org. Chem.* **2010**, *75*, 627. (c) Cho, H.; Sugimoto, K.; Iwama, Y.; Mitsuhashi, N.; Okano, K.; Tokuyama, H. *Heterocycles* **2011**, *82*, 1633. (d) Cho, H.; Iwama, Y.; Mitsuhashi, N.; Sugimoto, K.; Okano, K.; Tokuyama, H. *Molecules* **2012**, *17*, 7348.
- Abe, F.; Yamauchi, T. *Phytochemistry* **1994**, *35*, 169.
- (a) Gan, C.-Y.; Low, Y.-Y.; Thomas, N. F.; Kam, T.-S. *J. Nat. Prod.* **2013**, *76*, 957. (b) This compound was also isolated by Luo and co-workers from another *Apocynaceae* plant, *Alstonia scholaris* and was named as (–)-scholarisine G: Feng, T.; Cai, X.-H.; Zhao, P.-J.; Du, Z.-Z.; Li, W.-Q.; Luo, X.-D. *Planta Med.* **2009**, *75*, 1537.
- Feng, T.; Cai, X.-H.; Liu, Y.-P.; Li, Y.; Wang, Y.-Y.; Luo, X.-D. *J. Nat. Prod.* **2010**, *73*, 22.
- Van der Ende, A. E.; Kravitz, E. J.; Harth, E. *J. Am. Chem. Soc.* **2008**, *130*, 8706.
- Ashimori, A.; Bachand, B.; Calter, M. A.; Govek, S. P.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6488.
- Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485.
- Movassaghi, M.; Schmidt, M. A.; Ashenhurst, J. A. *Org. Lett.* **2008**, *10*, 4009.
- Downey, C. D.; Fleisher, A. S.; Rague, J. T.; Safran, C. L.; Venable, M. E.; Pike, R. D. *Tetrahedron Lett.* **2011**, *52*, 4756.
- Barton, D. H. R.; McCombie, S. W. *JCS, Perkin Trans. 1* **1975**, 1574.

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