Organic LETTERS

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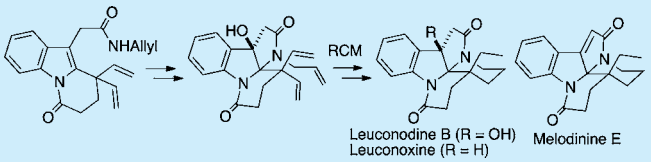
Total Syntheses of Leuconoxine, Leuconodine B, and Melodinine E by Oxidative Cyclic Aminal Formation and Diastereoselective Ring-Closing Metathesis

Atsushi Umehara, Hirofumi Ueda, and Hidetoshi Tokuyama*

Graduate School of Pharmaceutical Sciences, Tohoku University, Aoba 6-3, Aramaki, Aoba-ku, Sendai 980-8578, Japan

Supporting Information

ABSTRACT: Total syntheses of leuconodine B, melodinine E, and leuconoxine were accomplished via a divergent route. The [5.5.6.6]diazafenestrane skeleton was constructed from an indole-3-acetamide derivative via DMDO oxidation to hydroxylindolenine, TMSOTf/2,6-lutidine mediated cyclic aminal formation, and diastereoseletive ring-closing metathesis of a triene derivative.



Plants of the genus *Leuconotis*, such as *L. eugenifolia* and *L. griffithii* inhabiting Indonesia and Peninsular Malaysia, provide structurally diverse monoterpene indole alkaloids. Among them, leuconoxine (**1**),[1] isolated from *L. eugenifolia*, leuconodine B (**2**)[2] (a.k.a. scholarisine G[2b]), isolated from *L. griffithii*, and the related compound, melodinine E (**3**),[3] isolated from other genus *Melodinus henryi* Craib., possess an unprecedented [5.5.6.6]diazafenestrane skeleton containing an aminal functionality and a quaternary carbon center (Figure 1).

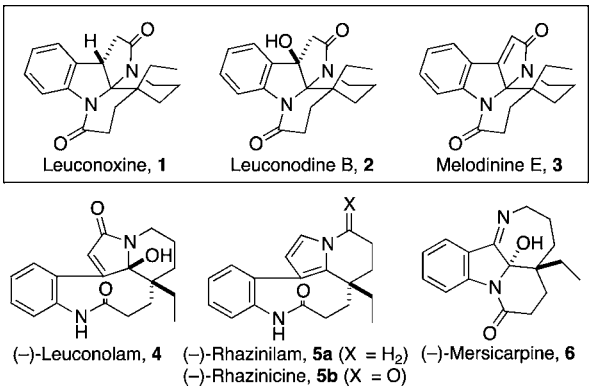


Figure 1. Structures of leuconoxine, rhazinilam, mersicarpine, and their congeners.

In addition to their intriguing structures, these compounds have attracted considerable attention from a biosynthetic point of view.[4] Thus, it was suggested that these compounds would be biosynthesized from *Aspidosperma* alkaloids,[5] through leuconolam (**4**), which is related to antitumor (−)-rhazinilam (**5a**).[6−9] Furthermore, Kam and co-workers proposed that melodinine E (**3**) would be biogenetically converted to (−)-mersicarpine (**6**),[10−12] which possesses an unusual azepino[3,2-*b*]indole ring system. We became interested in the highly diverse ring systems, as well as the proposed biosynthetic interrelationship of these monoterpene indole alkaloids, and initiated a research program.

So far, we have completed the total syntheses of (−)-rhazinilam (**5a**) and (−)-rhazinicine (**5b**) by utilizing our originally developed gold-catalyzed cascade double cyclization.[8i] In addition, a concise total synthesis of (−)-mersicarpine (**6**) was achieved by employing regiospecific reductive ring expansion of cyclic oxime with DIBALH for key construction of an azepino[3,2-*b*]indole skeleton.[11f,g] Recently, Zhu and co-workers established an elegant unified synthesis to provide (−)-leuconoxine (**1**), (−)-leuconodine B (**2**), (+)-melodinine E (**3**), (−)-leuconolam (**4**), and (−)-mersicarpine (**6**).[12] Herein we describe the total syntheses of leuconoxine (**1**), leuconodine B (**2**), and melodinine E (**3**) via a divergent route featuring an oxidative cyclic aminal formation and a diastereoselective ring-closing metathesis.

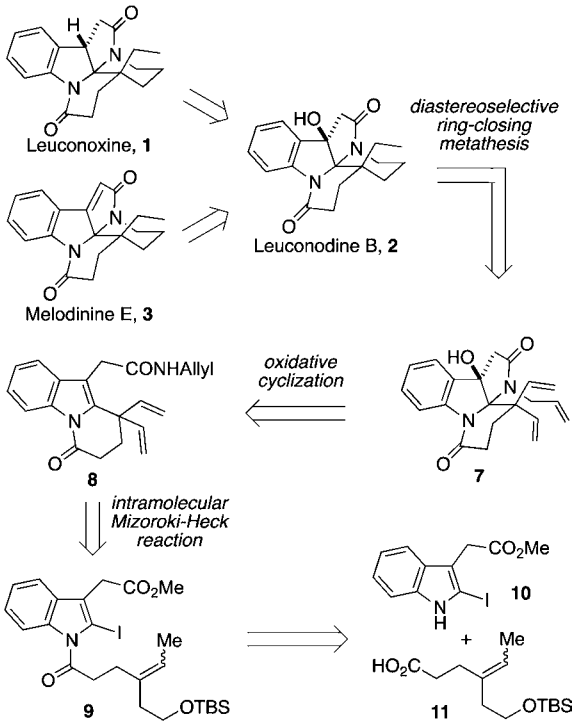
A retrosynthetic analysis is outlined in Scheme 1. Considering that leuconoxine (**1**) and melodinine E (**3**) should be easily derived from leuconodine B (**2**) by deoxygenation and dehydration, respectively, we designed a divergent route to these compounds via leuconodine B (**2**) as a pivotal intermediate. We envisioned that the characteristic [5.5.6.6]-diazafenestrane skeleton would be constructed by sequential cyclizations including an oxidative cyclic aminal formation[13] using indole-3-acetamide **8** and a diastereoselective ring-closing olefin metathesis using triene **7**.[14] The quaternary *gem*-divinyl carbon center on the indole C2 position of compound **8** would be constructed via an intramolecular Mizoroki−Heck reaction[15] of *N*-acyl-2-iodoindole **9** having an ethylidene moiety on the acyl chain. *N*-Acylindole **9** should be readily assembled by condensation of 2-iodoindole-3-acetate **10**[16] with carboxylic acid **11**.

The synthesis commenced with preparation of *N*-acylindole-3-acetate **9** (Scheme 2). Baeyer−Villiger oxidation of 1,4-

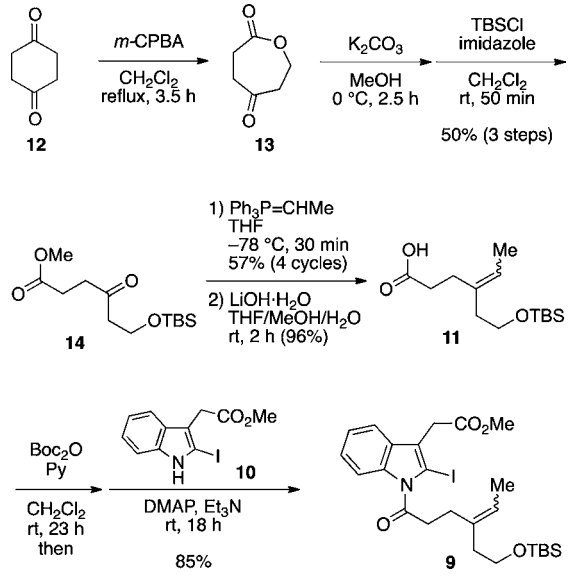
Received: March 26, 2014
Published: April 22, 2014

dx.doi.org/10.1021/ol500903e | *Org. Lett.* 2014, 16, 2526−2529

Scheme 1. Retrosynthetic Analysis



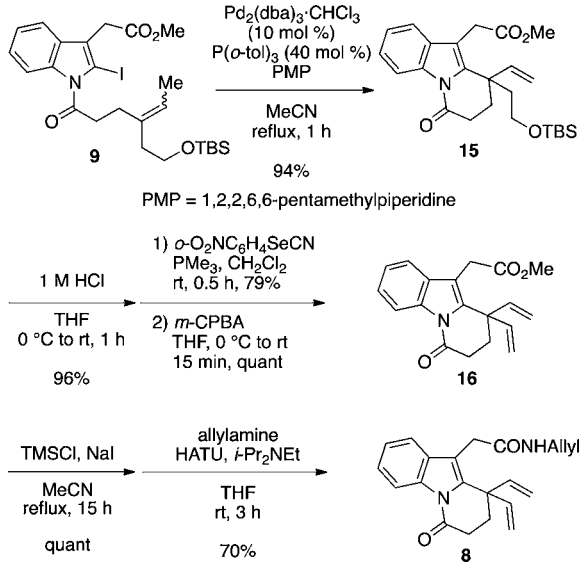
Scheme 2. Preparation of *N*-Acylindole 9



cyclohexanedione (**12**) with *m*-CPBA[17] gave ketolactone **13**, which was converted to ketoester **14**[18] by methanolysis and protection of the resultant alcohol as TBS ether. Wittig reaction of ketoester **14** was not straightforward and required careful optimizations. The desired ethylidene product was obtained as an *E*/*Z* mixture in 39% yield at best with recovery of **14** (37%) when the reaction was carried out at −78 °C. After the reaction proceeded through four cycles, an ethylidene product was obtained in 57% total yield, which was then saponified with $LiOH·H_2O$ to provide carboxylic acid **11**. Unexpectedly, condensation of carboxylic acid **11** with 2-iodoindole-3-acetate **10** under the conventional dehydration conditions or using the corresponding acid chloride resulted in poor yields. After extensive optimizations, we found that treatment of **11** with Boc_2O followed by addition of **10** in the presence of DMAP and Et_3N was effective to furnish the desired acylindole **9** in a good yield.

An intramolecular Mizoroki−Heck reaction of **9** in the presence of $Pd_2(dba)_3·CHCl_3$, P(*o*-tol)$_3$, 1,2,2,6,6-pentamethylpiperidine (PMP) proceeded smoothly to provide the expected *δ*-lactamindole **15** in a satisfactory yield with concomitant formation of a quaternary carbon center (Scheme 3).[11g,15,19]

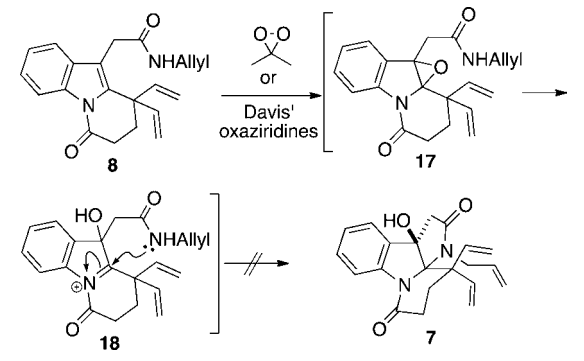
Scheme 3. Construction of Quaternary Carbon Center and Conversion to Indole-3-acetamide 8



The *gem*-divinyl group was then formed by removing the TBS group and subsequent dehydration of the resultant primary alcohol by the Grieco−Nishizawa protocol.[20] Finally, methyl ester **16** was converted to *N*-allylamide **8** by demethylation using a combination of TMSCl and NaI and condensation of the resultant carboxylic acid with allylamine in the presence of HATU and Hünig's base.

Having prepared the indole-3-acetamide **8** in hand, we then turned to the crucial oxidative cyclic aminal formation. Treatment of **8** with DMDO[21] or Davis' oxaziridines[22] as oxidants did not promote the expected sequential oxidative cyclization starting from the oxidation of the indole C2−C3 bond, ring opening, and cyclization to form the cyclic aminal product **7**. However, the starting compound **8** was simply recovered (Scheme 4). The low reactivity of **8** toward oxidants should be attributed to an insufficient electron density of the

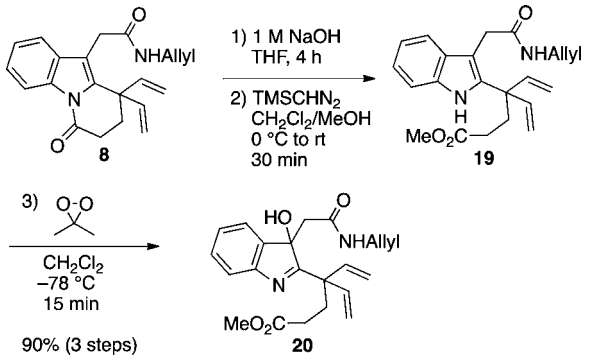
Scheme 4. Attempts for Oxidative Cyclization



dx.doi.org/10.1021/ol500903e | *Org. Lett.* 2014, 16, 2526−2529

indole ring, so we decided to cleave the lactam ring and examined the oxidation reaction. Thus, methyl ester **19**, which was obtained by treating **8** with sodium hydroxide and subsequently with trimethylsilyldiazomethane, was subjected to DMDO oxidation (Scheme 5). The expected oxidation of

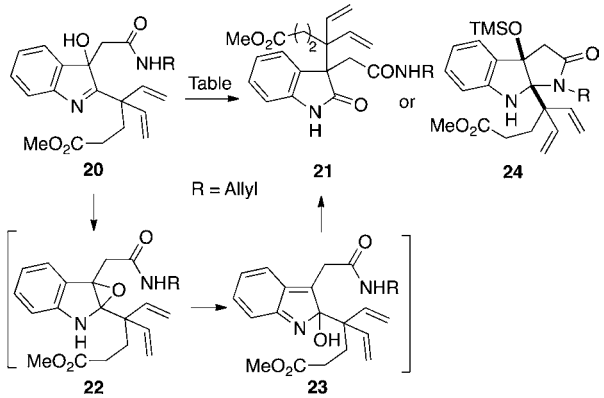
Scheme 5. Preparation of Hydroxyindolenine 20



the indole C2−C3 bond proceeded smoothly at −78 °C to afford hydroxyindolenine **20** in a high yield. Unfortunately, the following intramolecular aminal formation did not take place, despite an elevated reaction temperature and prolonged reaction time.

The failure of the sequential oxidative aminal cyclization prompted us to establish a stepwise protocol for cyclic aminal formations. A possible side reaction during the cyclization of a hydroxyindolenine such as **20** is a rearrangement reaction to afford a 3,3-disubstituted oxindole derivative, which was reported by Movassaghi et al.[23] As anticipated, the treatment of hydroxyindolenine **20** with $BF_3{\cdot}Et_2O$ gave 3,3-disubstituted oxindole **21** with recovery of starting compound **20** (Table 1, entry 1). It was proposed that the rearrangement was initiated by the formation of epoxide **22** and a subsequent ring opening to give **23**, followed by a semipinacol rearrangement to provide 3,3-disubstituted oxindole **21**.[23] A reaction using $Sc(OTf)_3$ also provided undesired oxindole **21** in 60% yield (entry 2). Given

Table 1. Optimization of Cyclic Aminal Formation

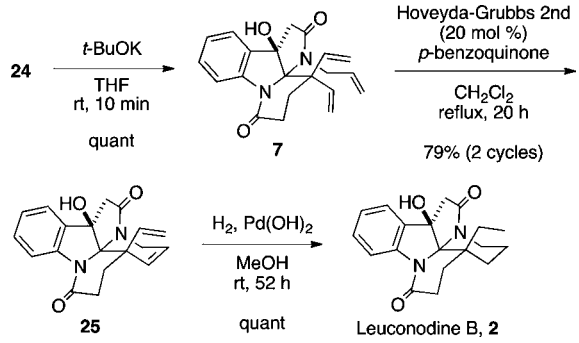


entry	reagents (equiv)	temp	time	yield (%) 21	24
1	$BF_3{\cdot}OEt_2$ (1.0)	0 °C to rt	3 h	20	0
2	$Sc(OTf)_3$ (1.0)	0 °C to rt	3 h	60	0
3	TMSOTf (2.05) 2,6-lutidine (2.05)	0 °C	5 min	0	93

the unsuccessful results, possibly due to the activation of the imine moiety with Lewis acids, we then turned to the activation of the amide moiety.[24] In fact, we have observed significant acceleration of the cyclic aminal formation upon treating hydroxyindolenine **20** with a combination of TMSOTf and 2,6-lutidine to afford the desired aminal product **24** in 93% yield without formation of oxindole **21** (entry 3).[25] We reasoned that the facile cyclization should be attributed to the formation of a sily imidate intermediate to enhance the inherent nucleophilicity of the amide moiety.[24]

The remaining task in synthesizing leuconodine B (**2**) was to construct the crucial [5.5.6.6]diazafenestrane framework by ring-closing metathesis. Before the key ring-closing metathesis was examined, the δ-lactam ring was formed by treating aminal **24** with *t*-BuOK with concomitant removal of the TMS group (Scheme 6). The expected ring-closing metathesis of triene **7**

Scheme 6. Total Synthesis of Leuconodine B (2)



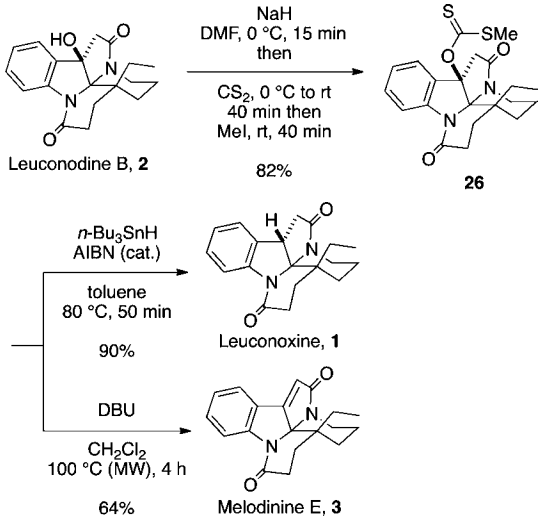
proceeded quite smoothly by heating with Hoveyda−Grubbs second generation[26] catalyst to furnish the pentacyclic[5.5.6.6]-diazafenestrane compound **25** as a sole isomer. The complete diastereoselectivity can be explained by starting with the reaction at the *N*-allyl moiety, followed by a ring-closing metathesis with one of the two vinyl groups to form a more thermodynamically stable piperidine ring. Finally, a total synthesis of leuconodine B (**2**) was completed by hydrogenation of two olefinic bonds.

Having established a synthetic route to leuconodine B (**2**), we then focused our attention on converting the pivotal intermediate leuconodine B (**2**) to leuconoxine (**1**) and melodinine E (**3**) (Scheme 7). First, the hydroxy group in leuconodine B (**2**) was reductively removed through its xanthate. Thus, alcohol **2** was treated sequentially with sodium hydride, carbon disulfide, and iodomethane to obtain methyl xanthate **26**, which was subjected to standard Barton−McCombie deoxygenation to furnish leuconoxine (**1**). In addition, the elimination[12] reaction of xanthate **26** took place by employing DBU and microwave heating to afford melodinine E (**3**). The spectroscopic data of these synthetic compounds were identical to those reported in the literature.[3,6b,27]

In summary, we have accomplished divergent total syntheses of three monoterpene indole alkaloids: leuconoxine (**1**), leuconodine B (**2**), and melodinine E (**3**). For the construction of the characteristic [5.5.6.6]diazafenestrane skeleton, we have devised a strategy consisting of an oxidative cyclic aminal formation and a diastereoselective ring-closing metathesis.

dx.doi.org/10.1021/ol500903e | *Org. Lett.* 2014, 16, 2526−2529

Scheme 7. Total Syntheses of Leuconoxine (1) and Melodinine E (3)



■ ASSOCIATED CONTENT

Supporting Information

Experimental details and procedures, compound characterization data, copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This materials is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: tokuyama@mail.pharm.tohoku.ac.jp.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was financially supported by the Cabinet Office, Government of Japan through its Funding Program for Next Generation World-Leading Researchers (LS008), a Grant-in aid for Young Scientists (B) (24790003) (for H.U.), and Platform for Drug Discovery, Informatics, and Structural Life Science from the MEXT, Japan.

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(27) There are very small discrepancies in the NMR spectra between our synthetic leuconodine B (**2**) and natural or Zhu's synthetic compound (ref 12). Zhu reported the NMR spectra of **2** varied due to a small amount of water (ref 12).