Natural Product Synthesis

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Enantioselective Total Syntheses of (−)-Rhazinilam, (−)-Leucomidine B, and (+)-Leuconodine F

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Abstract: *A divergent total synthesis of three structurally distinct natural products from imine **9** was accomplished through an approach featuring: 1) a Pd-catalyzed decarboxylative cross-coupling, and 2) heteroannulation of **9** with bromoacetaldehyde and oxalyl chloride to give tetrahydroindolizine **6** and dioxopyrrole **7**, respectively. The former was converted into (−)-rhazinilam, while the latter was converted into (−)-leucomidine B and (+)-leuconodine F. A substrate-directed highly diastereoselective reduction of a sterically unbiased double bond by using a homogeneous palladium catalyst was developed. A self-induced diastereomeric anisochronism (SIDA) phenomenon was observed for leucomidine B.*

The natural products (−)-rhazinilam (**1**),[1] (−)-leucomidine B (**2**),[2] and (+)-leuconodine F (**3**)[3] are members of the monoterpene indole alkaloids (Figure 1). (−)-Rhazinilam (**1**), with its unique axially chiral tetracyclic structure and potent in vitro tubulin-binding properties,[4] has triggered substantial synthetic efforts.[5,6] Total syntheses of (−)-leucomidine B (**2**)[6] and (+)-leuconodine F (**3**)[7] have been reported and there have been recent efforts towards the synthesis of members of the leuconodine family of natural products, which have an unusual [5.5.6.6]diazafenestrane system.[7,8] Although architecturally distinct, with different ring connectivity and topology, these natural products are all biogenetically derived from vincadifformine (**4**). Cleavage of the C2–C7 and C2–C16 bonds were key steps for the conversion of **4** into **1** and **2**, respectively. On the other hand, formation of a N1–C21 bond from the rhazinilam-type intermediate afforded the skeleton of **3**.[2,9]

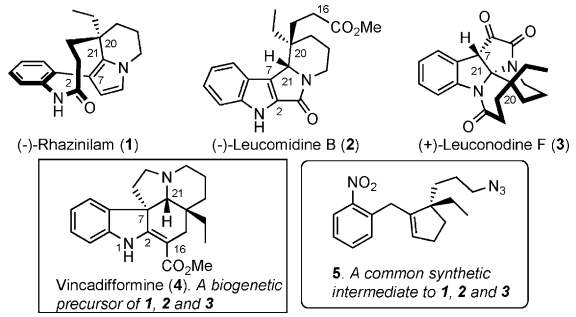
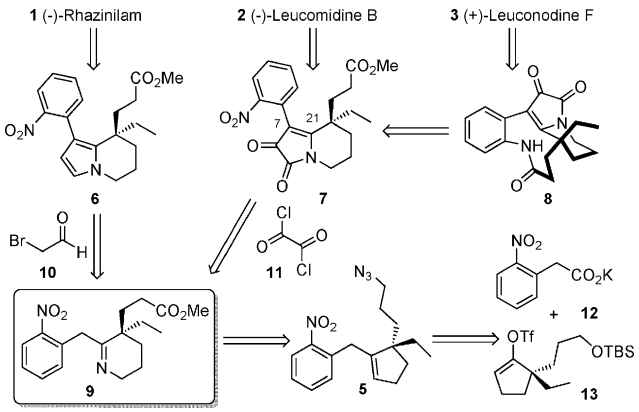


Figure 1. (−)-Rhazinilam (**1**), (−)-leucomidine B (**2**), and (+)-leuconodine F (**3**).

The ability of nature to synthesize a collection of structurally diverse natural products from a single intermediate has inspired chemists for years. We have recently developed a unified approach to (−)-rhazinilam (**1**) and (−)-leucomidine B (**2**).[6] The drawback of this approach was the lack of stereocontrol in the creation of the C21 stereogenic center of (−)-leucomidine B (**2**).[10] Indeed, the lack of diastereoselectivity in the nucleophilic addition of sterically unbiased α,α-disubstituted imines is a recurrent problem encountered in the synthesis of related indole alkaloids.[11] We report herein a new strategy that allowed us to accomplish the total syntheses of (−)-rhazinilam (**1**), (−)-leucomidine B (**2**), and (+)-leuconodine F (**3**) from a cyclopentene derivative **5** with complete control of stereoselectivity.

Our retrosynthetic analysis of **1**, **2**, and **3** is shown in Scheme 1. In a forward sense, we envisaged reaching the bicycles **6** and **7** through heteroannulation of tetrahydropyridine **9** with bromoacetaldehyde (**10**) and oxalyl chloride (**11**), respectively. While tetrahydroindolizine **6** has been converted into rhazinilam (**1**), reductive amination of **7** was expected to afford leucomidine B (**2**). The key issue to be addressed would be control of the C21 stereochemistry. Selective reduction of the nitro group in **7** without triggering the indolization, followed by macrolactamization would furnish **8**, which, upon transannular cyclization, would provide leuco-



Scheme 1. A unified synthetic approach to (−)-rhazinilam (**1**), (−)-leucomidine B (**2**), and (+)-leuconodine F (**3**).

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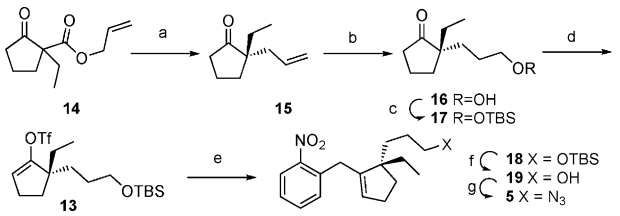
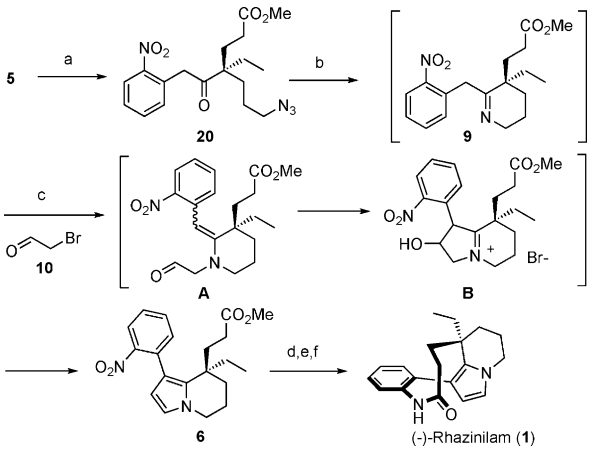
nodine F (**3**). The imine **9** should be accessible through structural reorganization of cyclopentene **5** through ozonolysis and subsequent tandem Staudinger/Aza–Wittig reaction. The cyclopentene **5** could in turn be synthesized through a palladium-catalyzed decarboxylative coupling between the potassium carboxylate **12** and the vinyl triflate **13**.[12]

Synthesis of enantiomerically enriched 1,5,5-trisubstituted cyclopentene **5** is detailed in Scheme 2. Pd-catalyzed asymmetric decarboxylative allylation of the known β-ketoester **14** according to Stoltz' method afforded (*S*)-2-allyl-2-ethylcyclopentan-1-one (**15**) in 87% yield with 86% *ee*.[13] Hydroboration of **15** followed by oxidation of the resulting alkylborane provided primary alcohol **16**, which, without purification, was directly converted into TBDMS ether **17** in 85% overall yield. Deprotonation of ketone **17** followed by trapping of the resulting enolate with *N*-phenylbis(trifluoromethanesulfonimide) afforded the desired vinyl triflate **13** in 92% yield. The decarboxylative coupling of **13** with potassium carboxylate **12** afforded **18** in 52% yield in spite of the steric hindrance around the vinyl triflate unit. Treatment of a methanol solution of **18** with a catalytic amount of in situ generated hydrochloric acid[14] afforded alcohol **19**, which was transformed into azide **5** via the mesylate intermediate.



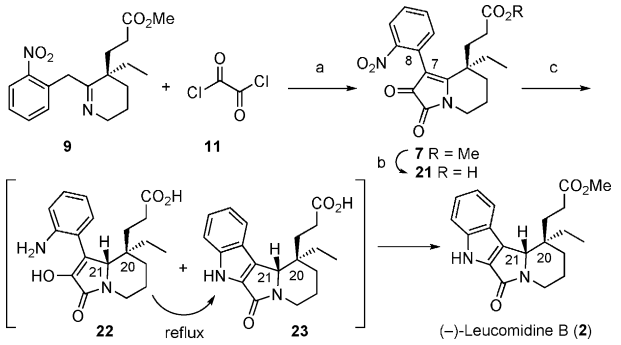
Scheme 2. Synthesis of cyclopentene **5**. a) $[Pd_2(dba)_3]$ (2.5 mol%), (*S*)-*t*BuPHOX (6.25 mol%), THF (*c* 0.067 M), 25°C, 3 h, 87% yield, 86% *ee*; b) disiamyl borane (2.5 equiv), THF, 0°C to RT, 2 h then H_2O_2/NaOH, RT, 1 h; c) TBSCl (1.2 equiv), imidazole (1.5 equiv), DMF, RT, 12 h, 85% over 2 steps; d) LiHMDS (1.1 equiv), THF, −78°C, 45 min then $PhNTf_2$ (1.2 equiv), −78°C to RT, 12 h, 92%; e) potassium 2-(2-nitrophenyl)acetate (**12**, 2.5 equiv), $[\{Pd(allyl)Cl\}_2]$ (5 mol%), XPhos (15 mol%), diglyme, 140°C, 2 h, 52%; f) AcCl (0.20 equiv), MeOH, RT, 1 h; g) MsCl (1.2 equiv), Et_3N (1.5 equiv), DMF, RT, 5 h then NaN_3 (3.0 equiv), RT, 12 h, 84% over 2 steps. dba = 1,5-diphenyl-1,4-pentadien-3-one, THF = tetrahydrofuran, TBS = *tert*-butyldimethylsilyl, DMF = *N*,*N*-dimethylformamide, LiHMDS = lithium hexamethyldisilazide, Tf = triflate.

Conversion of cyclopentene **5** into (−)-rhazinilam (**1**) is depicted in Scheme 3. Ozonolysis of cyclopentene **5** in CH_2Cl_2/MeOH solution buffered with $NaHCO_3$, followed by treatment of the crude ozonolysis product with acetic anhydride and triethylamine,[15] afforded the keto ester **20** in 92% yield. The one-pot Staudinger reduction/cyclization of **20** (MeCN, 70°C, 3 days) provided the tetrahydropyridine **9** in 86% isolated yield. We noted that imine **9** was sufficiently stable to be purified by flash column chromatography. While condensation of 1-alkyl-3,4-dihydroisoquinolines with α-halo ketones has been exploited for the synthesis of pyrrolo[2,1-a]isoquinolines,[16] heteroannulation of imines with bromoacetaldehyde has, to the best of our knowledge, never been examined. After much experimentation, we were pleased to find that simply stirring an acetonitrile solution of **9** and bromoacetaldehyde (**10**)[17] at 70°C in the presence of a weak base ($NaHCO_3$) afforded tetrahydroindolizine **6** in excellent yield. Mechanistically, the reaction might be initiated by *N*-alkylation to give enamine aldehyde **A**, which undergoes cyclization to give **B**. Dehydration of **B** followed by tautomerization would afford tetrahydroindolizine **6**. We subsequently found that the Staudinger reduction/Aza–Wittig and heteroannulation can be integrated into a one-pot reaction to allow the direct conversion of **20** into **6** in 76% yield. Finally, compound **6** was transformed into (−)-rhazinilam (**1**) in 79% overall yield by following the standard reduction/hydrolysis/macrolactamization sequence[6].



Scheme 3. Total synthesis of (−)-rhazinilam (**1**). a) O_3, $NaHCO_3$ (0.30 equiv), CH_2Cl_2/MeOH (4/1), −78°C, 2 min, then Ac_2O (4.0 equiv), Et_3N (2.0 equiv), 0°C to RT, 3 h, 92%; b) PPh_3 (1.1 equiv), CH_3CN, 70°C, 3 days; c) bromoacetaldehyde [**10**, 5.0 equiv, freshly prepared as a dichloromethane solution (49 wt%)], $NaHCO_3$ (6.0 equiv), 70°C, 6 h, 76% from **20**; d) H_2, Pd/C, MeOH, RT, 30 min; e) KOH, MeOH/H_2O, RT, 12 h; f) EDCI, HOBt, Et_3N, CH_2Cl_2, RT, 3 h, 79% over 3 steps. EDCI = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, HOBt = 1-hydroxybenzotriazole.

The total synthesis of (−)-leucomidine B (**2**) is shown in Scheme 4. Cyclocondensation between imine **9** and oxalyl chloride (**11**, 1.1 equiv) in the presence of Et_3N afforded the desired dioxopyrrole **7** in quantitative yield after acidic workup.[18] Owing to hindered rotation around the C7–C8 bond, compound **7** was isolated as a mixture of two inseparable atropisomers. While indolization of **7** to give natural product **2** proceeded without problems under a variety of reductive conditions, control of the diastereoselectivity turned out to be challenging owing to the insignificant steric difference between the neighboring ethyl and 2-methoxycarbonylethyl groups. For example, heterogeneous catalytic hydrogenation of **7** in the presence of Pd/C afforded (−)-leucomidine B (**2**) and its C21 epimer in a 1:1 ratio. A similar result was obtained by using aqueous $TiCl_3$ as the reductant.[19] The reagent-controlled enantioselective reduction of **7** was also examined. CuH-catalyzed 1,4-reduction with Ph_2SiH_2 as the reducing agent in the presence of a variety of chiral ligands afforded the 1,4-reduction product in excellent yield,[20] but the diastereoselectivity never exceeded 1.3:1.



Scheme 4. Total synthesis of (−)-leucomidine B (**2**). a) Et_3N (2.5 equiv), CH_2Cl_2, 0 °C to RT, 1 h, quantitative; b) KOH, THF/H_2O, 87 %; c) H_2 (1 atm), $Pd(TFA)_2$ (10 mol %), CF_3CH_2OH, 0 °C to RT, 12 h; then reflux; then $TMSCHN_2$ (5.0 equiv), 0 °C, 15 min, 71 % from **21**. TFA = trifluoroacetic acid, TMS = trimethylsilyl.

The substrate-directed diastereoselective reduction was next examined by taking advantage of the coordinating ability of the carboxylic acid group. Hydrogenation (1.0 atm H_2) of carboxylic acid **21** in the presence of Crabtree's catalyst or hydride reduction with Stryker's reagent CuH/Ph_2SiH_2 led only to recovery of the starting material. Gratifyingly, treatment of a trifluoroethanol (TFE) solution of **21** with $Pd(TFA)_2$ under hydrogen atmosphere (1.0 atm)[21] at 0 °C afforded a mixture of aniline **22** and indole **23**, which, after heating to reflux, was converted into a single compound **23** with a diastereomeric ratio of 92:8. Addition of an excess of $TMSCHN_2$ (5.0 equiv) to the above reaction mixture at 0 °C furnished, after column chromatography, the diastereomerically pure (−)-leucomidine B (**2**) in 71 % isolated yield. As expected, reduction of ester **7** under identical conditions afforded leucomidine B (**2**) and its C21 epimer without noticeable diastereoselectivity owing to the poor coordinating ability of the ester function.[22] It is worth noting that hydrogenation of **21** in the presence of Pd/C or $Pd(OH)_2/C$ afforded a 1:1 diastereomeric mixture of tetracycle **23**. We also synthesized the (±)-leucomidine B (**2**) by following the same synthetic route and obtained an X-ray crystal structure of (±)-**2** that confirmed the relative stereochemistry between C20 and C21. A heterodimer was formed in the crystal packing of (±)-**2** (Figure 2),[23] which nicely explains the concentration dependence of the $[\alpha]_D$ value of our enantiomerically enriched (−)-**2** in apolar solvent [89 % *ee*, $[\alpha]_D = -21$ (*c* 1.0, $CHCl_3$) $[\alpha]_D = -29$ (*c* 0.3, $CHCl_3$); lit.[2] $[\alpha]_D = -18$ (*c* 0.3, $CHCl_3$)].[24] In addition, a self-induced diastereomeric anisochronism (SIDA) phenomenon was observed for leucomidine B (see the Supporting Information).[7,25]

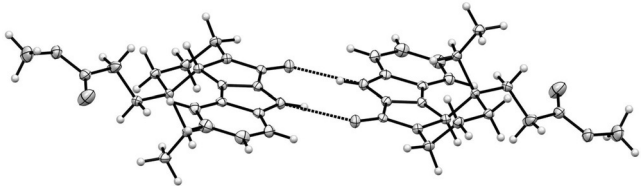
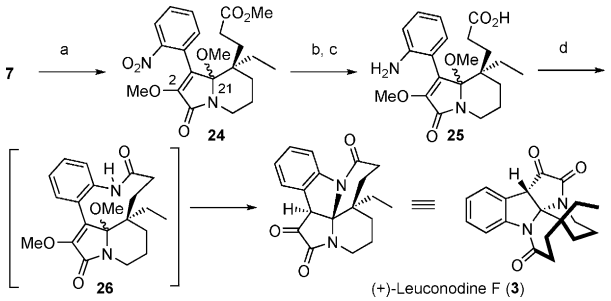


Figure 2. X-ray structure of (±)-leucomidine B (**2**).

To reach (+)-leuconodine F (**3**) from **7**, we needed to chemoselectively reduce the nitro group without touching the 2,3-dioxopyrrole and to avoid condensation of the resulting aniline with the neighboring carbonyl function. Owing to the high electrophilicity of the dioxopyrrole unit,[26] masking the carbonyl unit was deemed necessary and 1,4-conjugate addition of methanol to β,γ-unsaturated α-keto amide was thought to be ideal. The resulting adduct would be sufficiently stable under the neutral or mild basic conditions planned for the macrolactamization but the electrophilicity of C2 and C21 are readily revealed under acidic conditions for the subsequent transannular cyclization.

The realization of the aforementioned synthetic plan is shown in Scheme 5. Stirring a methanol solution of **7** in the presence of DIPEA at room temperature, followed by trapping of the resulting enol with an excess amount of



Scheme 5. Total synthesis of (+)-leuconodine F (**3**). a) DIPEA, MeOH, RT, 1 h, then $TMSCHN_2$, 0 °C to RT, 30 min, 93 %; b) KOH, MeOH/H_2O, RT, 12 h; c) H_2, Pd/C, MeOH, RT, 1 h; d) EDCI, HOBt, Et_3N, CH_2Cl_2, RT, 12 h, then TFA, RT, 4 h, 53 % from **24**. DIPEA = diisopropylethylamine.

trimethylsilyldiazomethane afforded exclusively the 1,4-adduct **24** in 93 % yield of isolated product (Scheme 5). Saponification of the methyl ester followed by hydrogenation of the nitro group furnished amino acid **25**, which, without purification, underwent EDCI-mediated lactamization to provide **26** as a mixture of diastereomers. Upon addition of TFA to the above mixture, a highly diastereoselective transannular cyclization took place to afford (+)-leuconodine F (**3**) as a single diastereomer in 53 % overall yield from **24**. The physical and spectroscopic data for our synthetic compound were identical to those reported for the natural product.

In conclusion, we developed a novel divergent total synthesis of three natural products, namely (−)-rhazinilam (**1**, 12 steps, 16.4 % overall yield), (−)-leucomidine B (**2**, 12 steps, 14.5 % overall yield), and (+)-leuconodine F (**3**, 14 steps, 11.6 % overall yield) from readily available (±)-allyl 1-ethyl-2-oxocyclopentane-1-carboxylate (**14**). Heteroannulation of tetrahydropyridine **9** with bromoacetaldehyde (**10**) and oxalyl chloride (**11**), respectively, was successfully developed for the construction of the functionalized bicycles, which were subsequently diverged to three skeletally different natural products. A homogeneous palladium catalyst was exploited for the first time to accomplish a substrate-directed highly diastereoselective hydrogenation of a sterically unbiased double bond. We anticipate that this method will find applications in the synthesis of other monoterpene indole alkaloids.

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Keywords: asymmetric synthesis · divergent synthesis · domino cyclization · heteroannulation · indole alkaloids

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