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Total Syntheses of (−)-Mersicarpine, (−)-Scholarisine G, (+)-Melodinine E, (−)-Leuconoxine, (−)-Leuconolam, (−)-Leuconodine A, (+)-Leuconodine F, and (−)-Leuconodine C: Self-Induced Diastereomeric Anisochronism (SIDA) Phenomenon for Scholarisine G and Leuconodines A and C

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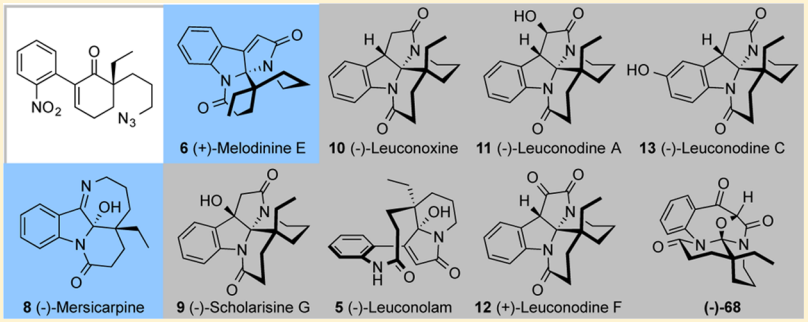
Supporting Information



ABSTRACT: Enantioselective total syntheses of title natural products from a common cyclohexenone derivative (*S*)-**18** were reported. Ozonolysis of (*S*)-**18** afforded a stable diketo ester (*R*)-**17** that was subsequently converted to two skeletally different natural products, i.e., (−)-mersicarpine (**8**) with a [6.5.6.7] fused tetracyclic ring system and (−)-scholarisine G (**9**) with a [6.5.6.6.5] fused pentacyclic skeleton, respectively. The postcyclization diversification was realized by taking advantage of the facile conversion of (+)-melodinine E (**6**) to *N*-acyliminium ion **7**, from which a hydroxy group was selectively introduced to the C6, C7, C10 and the central C21 position of diazafenestrane system, leading to (−)-leuconodine A (**11**), (+)-leuconodine F (**12**), (−)-scholarisine G (**9**), (−)-leuconodine C (**13**), and skeletally different (−)-leuconolam (**5**). Furthermore, an unprecedented non-natural oxabridged oxadiazafenestrane **68** was formed by oxidation of (+)-melodinine E (**6**). During the course of this study, a strong self-induced diastereomeric anisochronism (SIDA) phenomenon was observed for scholarisine G (**9**), leuconodines A (**11**) and C (**13**). X-ray structures of both the racemic and the enantiopure natural products **9**, **11**, and **13** were obtained. The different crystal packing of these two forms nicely explained the chemical shift differences observed in the ^{1}H NMR spectra of the racemic and the enantio-enriched compounds in an achiral environment.

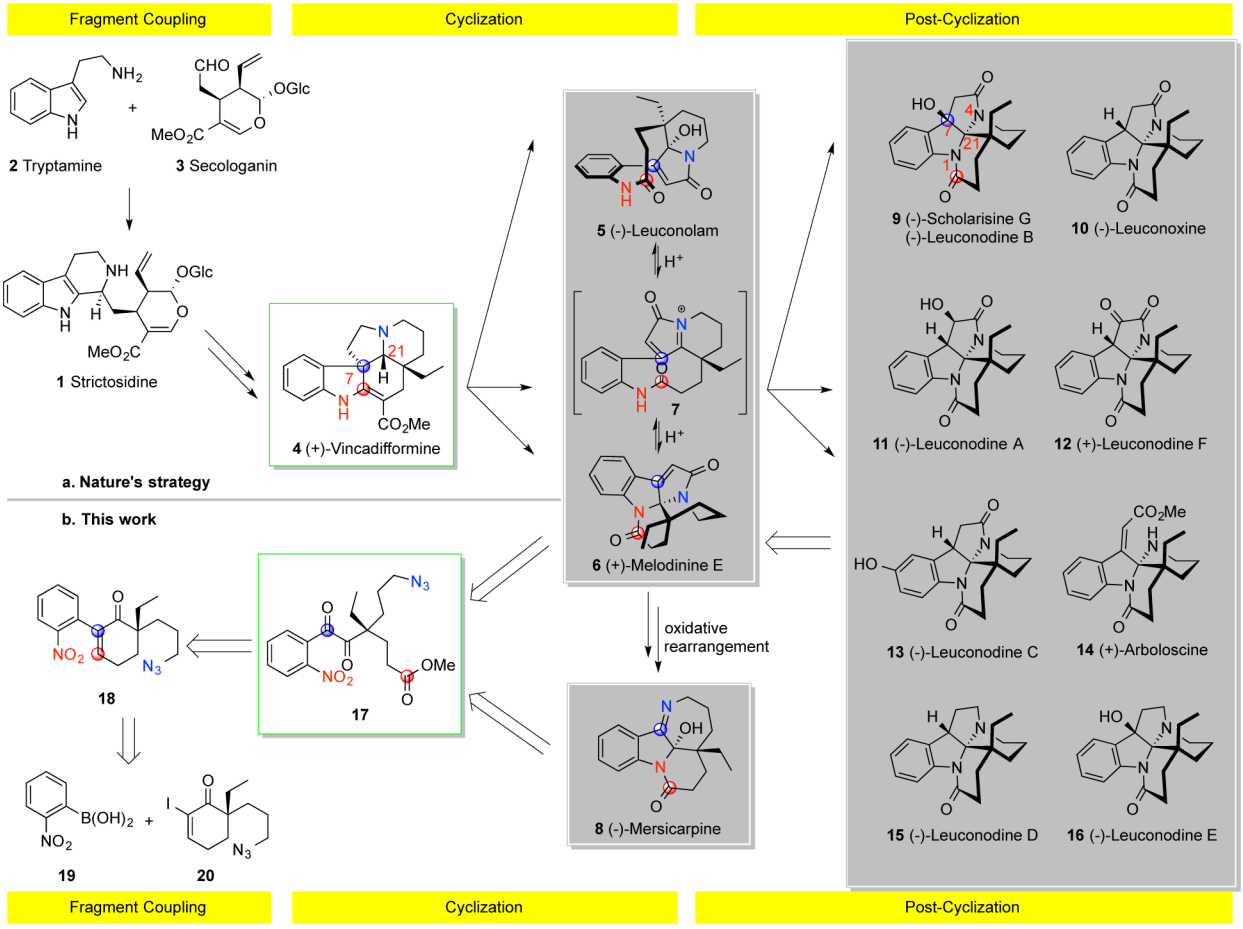
INTRODUCTION

The monoterpene indole alkaloids represent an important family of natural products for their potent bioactivities and structural diversities.[1] Until now, over 2000 members with more than 42 different skeletons are known.[2] Despite the structural complexity and diversity, they are uniformly made by nature's biosynthetic machineries from strictosidine (**1**), which is in turn produced by fragment coupling of two simple building blocks, tryptamine (**2**) and secologanin (**3**) by way of the Pictet-Spengler reaction (Scheme 1a).[3] Inspired by nature's simple logic, namely couple and divert, for making skeletally diverse alkaloids, we initiated a research program aimed at mimicking the biosynthetic philosophy of nature at strategic level by using the synthetic tools available in the laboratory. As a proof-of-concept,[4] we recently accomplished total synthesis of vincadifformine (**4**),[5] goniomitine and kopsihainanine A, three polycyclic natural products with different ring connectivities and stereochemistry, from readily accessible intermediates. Two key steps characterized our approaches: (a) a Pd-catalyzed decarboxylative coupling between phenyl acetate derivatives and vinyl triflates; (b) an *i*ntegrated *O*xidation/*R*eduction/*C*yclization (*i*ORC) process that completely reorganized cyclopentene derivatives to the polycyclic skeletons of targeted natural products. By imposing certain geometric constraints into the *i*ORC substrates, we demonstrated that it is possible to control the chemo- and stereoselectivity of the complex domino process to deliver specifically the desired natural product.

Received: April 7, 2015
Published: May 6, 2015

DOI: 10.1021/jacs.5b03619
J. Am. Chem. Soc. 2015, 137, 6712−6724

Scheme 1. Logic for the Synthesis of Monoterpene Indole Alkaloids: (a) Nature's Strategy; (b) Our Approach



To further explore the synthetic potential of this concept in natural product synthesis, we became interested in addressing following two additional criteria that nature has used extensively in their biosynthesis machineries for structural diversification:[6] (a) to reach condition-controlled diversification from the same intermediate rather than the substrate-controlled cyclization; (b) to reach structural diversity by selectively converting one intermediate/natural product to a series of natural products with different skeletons and/or different oxidation states. Toward this goal, the group of leuconolam-leuconoxine-mersicarpine alkaloids belonging to the *Aspidosperma* subfamily[7] was chosen to showcase our strategy.[8]

(−)-Leuconolam (**5**), with a fused [6.9.6.5] ring system, was first isolated from *Leuconotis griffithii* in 1984 by Goh and co-workers.[9] Derived from the oxidative rearrangement of vincadifformine (**4**),[10] leuconolam was proposed to be the first intermediate in the biosynthesis of leuconolam-leuconoxine-mersicarpine class of alkaloids. The groups of Banwell[11] and of Hoye[12] have accomplished total syntheses of this natural product.

(+)-Melodinine E (**6**, a.k.a. 6,7-dehydroleuconoxine) has an interesting [6.5.6.6.5] fused pentacyclic ring system, four of which are arranged around the C21 aminal carbon. The structure of melodinine E was first reported by Luo and co-workers in 2007.[13] Kam and co-workers subsequently found that epileuconolam isolated from *Leuconotis eugenifolia* by Goh and co-workers in 1986 [10a] was actually identical to melodinine E.[14] It was proposed that melodinine E was biogenetically derived from leuconolam via transannular cyclization of the *N*-acyl iminium ion intermediate **7**. Related natural products such as (−)-scholarisine G[15] (**9**, a.k.a. leuconodine B[16]), (−)-leuconoxine[17] (**10**, a.k.a. diazaspiroleuconolam[18]), (−)-leuconodine A (**11**), (+)-leuconodine F (**12**, a.k.a. 6-oxoleuconoxine[19]), (−)-leuconodine C (**13**), (−)-leuconodine D (**15**), and (−)-leuconodine E (**16**),[16] as well as the secoleuconoxine, (+)-arboloscine (**14**),[20] have also been isolated from various plants during the past decades. All these natural products with different oxidation states are biosynthetically derived from melodinine E (**6**). Interestingly, structures with the same [6.5.6.6.5] fused pentacyclic ring skeleton were disclosed before the isolation of these natural products. Thus, treatment of N4-oxide of 1,2-dehydro-aspidospermidine[21] with acetic anhydride under Polonovski-Potier conditions afforded leuconodine D and rhazinilam/leuconolam skeleton.[22] On the other hand, treatment of leuconolam with a MeOH solution of HCl provided 6-chloroleuconoxine (initially named 6-chlorodiazaspiroleuconolam).[10a,b] Since our first enantioselective total syntheses of (+)-melodinine E (**6**), (−)-scholarisine G (**9**), and (−)-leuconoxine (**10**),[8] three racemic total syntheses from the group of Tokuyama,[23] Dai,[24] Stoltz and Liang[25] and two enantioselective total syntheses from the group of Higuchi and Kawasaki,[26] Gaich,[27] respectively, have been reported.

Isolated by Kam and co-workers in 2004 from the *Kopsia* genus, (−)-mersicarpine (**8**) was biosynthetically derived from melodinine E via an oxidative skeletal rearrangement.[28] The intriguing [6.5.6.7] fused tetracyclic skeleton was characterized by the unique tetrahydro-2*H*-azepine ring system, and became a popular target since its isolation. Eight total syntheses have

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been achieved by groups of Kerr,[29] Fukuyama,[30] Tokuyama,[31] Zhu,[8] Liang,[25,32] Han,[33] Dai[24] and Higuchi/Kawasaki,[26,34]

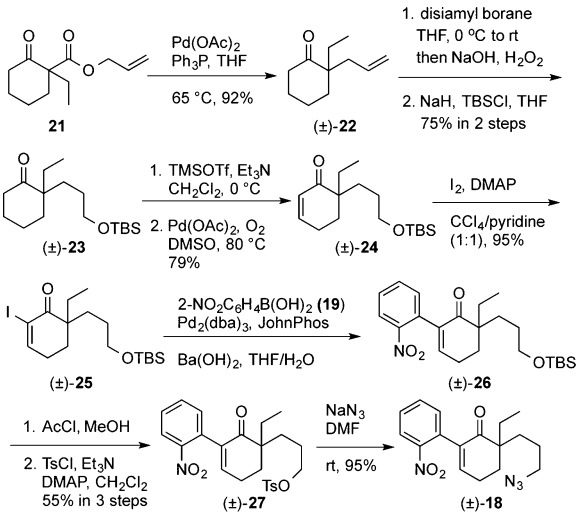
From vincadifformine (Scheme 1a), nature synthesized leuconolam (**5**) as the primary product that was subsequently elaborated to melodinine E (**6**), scholarisine G (leuconodine B, **9**), and leuconodines A, C, D, E. F (**11**, **13**, **15**, **16**, **12**) and mersicarpine (**8**). In our planned three-phase synthesis strategy (Scheme 1b), we selected scholarisine G (**9**) and mersicarpine (**8**) as our primary synthetic targets reasoning that the former could be easily dehydrated to melodinine E (**6**), which could in turn be elaborated to other leuconodines in the postcyclization phase. In the cyclization phase, both [6.5.6.7] fused tetracyclic skeleton in (−)-mersicarpine (**8**) and [6.5.6.6.5] fused pentacyclic ring system in (−)-scholarisine G (**9**) were thought to be obtained by controlling the cyclization mode (6-membered ring vs 7-membered ring) of the same diketo ester **17**, an ozonolysis product of substituted cyclohexenone derivative **18**. The latter could be obtained by the Suzuki−Miyaura cross-coupling reaction between 2-nitrophenyl boronic acid **19** and vinyl iodide **20** in the fragment coupling phase. We detail herein the total syntheses of (−)-mersicarpine (**8**), (−)-scholarisine G (**9**), and the successful transformation of the latter to (+)-melodinine E (**6**), (−)-leuconoxine (**10**), (−)-leuconolam (**5**), (−)-leuconodine A (**11**), (+)-leuconodine F (**12**) and (−)-leuconodine C (**13**) as well as other non-natural products resulting from unprecedented oxidative transformations. In addition to the enantiomerically enriched natural products, we have also synthesized the racemic form of these alkaloids and document the self-induced diastereomeric anisochronism (SIDA) phenomenon in the ^{1}H NMR spectra of scholarisine G (**9**), leuconodines A (**11**) and C (**13**). The different autoassociation modes in the solid state of both racemic and enantio-enriched natural products nicely explained the ^{1}H NMR spectra difference between the racemic mixture and the enantiomer in an achiral solvent.

RESULTS AND DISCUSSION

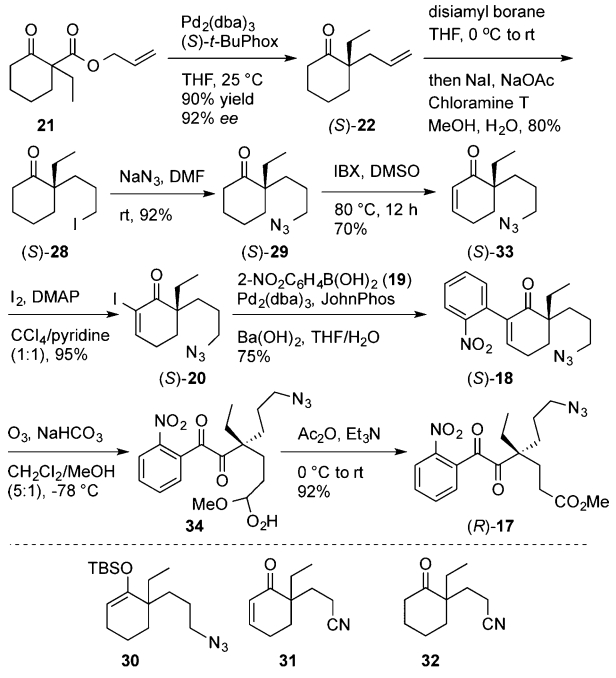
Fragment Coupling Phase: Synthesis of Functionalized Cyclohexenone 18. The synthesis of (±)-**18** commenced with palladium-catalyzed decarboxylative allylation of β-ketoester **21** (Scheme 2). With the use of the conditions developed by Tsuji and co-workers,[35] the keto ester **21** was converted to 2-allyl-2-ethyl cyclohexanone **22** in 92% yield. A hydroboration−oxidation sequence transformed **22** to the corresponding primary alcohol which, without purification, was directly protected as its TBS ether to give **23** (NaH, TBSCl, THF). No attempt was made to purify the primary alcohol as it readily cyclized to hemiketal upon purification by column chromatography on silica gel. The hemiketal was also the major product when the TBS protection was performed in DMF in the presence of imidazole.[36] Saegusa-Ito oxidation of cyclohexanone **23** [TMSOTf, Et_3N, CH_2Cl_2, then $Pd(OAc)_2$, O_2, DMSO] provided enone **24** in 79% yield.[37] α-Iodination of enone **24** occurred smoothly to afford vinyl iodide **25**, which underwent the Suzuki−Miyaura cross-coupling with 2-nitrophenylboronic acid (**19**) to give **26**.[38] Removal of the TBS silyl ether under mild acidic conditions (AcCl in MeOH),[39] followed by tosylation of the resulting primary alcohol, converted **26** to **27** in 55% overall yield in 3 steps. Reaction of **27** with sodium azide afforded the desired cyclization precursor (±)-**18** in 95% yield.

An enantioselective synthesis of (*R*)-**17** is shown in Scheme 3. Enantioselective decarboxylative allylation of β-keto ester **21** under Stoltz's conditions provided enantio-enriched α,α-disubstituted cyclohexanone (*S*)-**22** in 90% yield with 92% ee.[40] Taking advantage of a hydroboration−iodination sequence,[41] the terminal double bond in (*S*)-**22** was then transformed in one operation into alkyl iodide (*S*)-**28**, which was subsequently converted to alkyl azide (*S*)-**29** under standard conditions (NaN_3, DMF). Formation of silyl enol ether **30** followed by dehydrogenation with $Pd(OAc)_2$ in DMSO at 60 °C for 12 h afforded the desired enone in 70% yield in 200 mg scale.[37] The reaction needed to be carefully monitored as prolonged reaction time or over heating (above 80 °C) produced a significant amount of nitrile **31** resulting from the palladium-catalyzed dehydrogenation of alkyl azide.[42]

Scheme 2. Synthesis of (±)-18



Scheme 3. Enantioselective Synthesis of (*S*)-18 and Its Conversion to Diketo Ester (*R*)-17

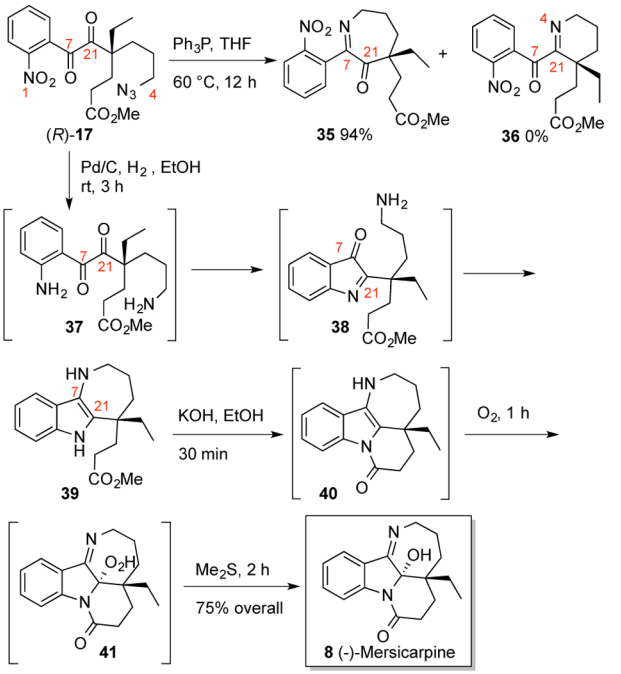


DOI: 10.1021/jacs.5b03619
J. Am. Chem. Soc. 2015, 137, 6712−6724

Unfortunately, when the reaction was performed in a gram scale, the reaction became sluggish affording low yield of the enone **33**. Heating the reaction mixture to 80 °C provided nitrile **32** in 55% isolated yield as the major product indicating that the dehydrogenation of alkyl azide to nitrile became kinetically competitive relative to the Saegusa-Ito oxidation of the silyl enol ether at this temperature. On the other hand, either silyl enol ether **30** or cyclohexanone **29** was recovered when oxidants other than O_2 were used.[43,44] Finally, it was found that oxidation of cyclohexanone **29** with an excess amount of IBX (6.0 equiv) in DMSO proceeded smoothly in multigram scale to provide enone (*S*)-**33** in 70% yield.[30,45] α-Iodination of (*S*)-**33** followed by Suzuki–Miyaura cross-coupling of the resulting vinyl iodide with 2-nitrophenyl boronic acid (**19**) afforded (*S*)-**18** without event. Cleavage of the enone double bond with ozone buffered with $NaHCO_3$ gave peroxide **34** cleanly as a mixture of 1:1 diastereomers, which was transformed to the methyl ester (*R*)-**17** by in situ addition of acetic anhydride and triethylamine.[46] This ozonolysis–oxidative workup sequence worked efficiently in multigram scale.

Cyclization Phase: Total Syntheses of (−)-Mersicarpine (8), (−)-Scholarisine G (9), and (+)-Melodinine E (6). The total synthesis of (−)-mersicarpine (**8**) from diketone (*R*)-**17** is shown in Scheme 4. It is reasonable to assume that after

Scheme 4. From Linear Diketone (*R*)-17 to [6,5,6,7]-Fused Tetracyclic Skeleton: A One-Pot Synthesis of (−)-Mersicarpine (8)



reduction of both the nitro and the azido groups, the condensation of aniline nitrogen (N1) with the C21 carbonyl group leading to indolenine structure would be both a kinetically and thermodynamically favored process, while the primary amine (N4) could attack either the C7 or the C21 carbonyl (or transient iminyl) groups leading to mersicarpine and leuconoxine skeleton, respectively. The result of a preliminary experiment under Staudinger conditions was revealing. Treatment of (*R*)-**17** with Ph_3P resulted in the formation of 7-membered azepino derivative **35** in 94% yield at the expense of the tetrahydropyridine **36**. The reasons for the preferential formation of 7-membered ring are two-fold. First, the C7 carbonyl group is more electrophilic due to the presence of an electron-withdrawing 2-nitrophenyl group. Second, the C7 is also sterically more accessible than the C21 carbonyl function, the latter being adjacent to a quaternary carbon. While compound **35** was certainly an attractive intermediate for further elaboration to mersicarpine, a more direct synthesis of natural product from (*R*)-**17** was sought. Gratefully, simply stirring an ethanol solution of (*R*)-**17** under hydrogen atmosphere in the presence of Pd/C (3 mol % based on Pd) gave, after column chromatography, (−)-mersicarpine (**8**) in 23% yield together with 50% of the hexahydroazepino[3,2-*b*]indole **39**. Reasoning that mersicarpine (**8**) could be formed by a sequence of lactamization and facile air-oxidation of 3-aminoindole **39**, a more efficient one-pot protocol allowing the direct conversion of (*R*)-**17** to (−)-mersicarpine (**8**) was developed. Hydrogenation of (*R*)-**17** in the presence of Pd/C (10 mol % based on Pd) gave unstable 3-aminoindole derivative **39**, which underwent KOH-promoted lactamization to give tetracyclic derivative **40** (see Supporting Information Figures S1 and S2 for detailed NMR studies of this sequence). Purging the reaction mixture with argon followed by oxygen afforded presumably peroxide **41**,[30,47] which, upon addition of dimethyl sulfide, was reduced to (−)-mersicarpine (**8**) in 75% overall yield. We stress that the whole transformation was realized by sequential addition of reagents (Pd/C, H_2; KOH; O_2; Me_2S) to the ethanol solution of diketone (*R*)-**17** without workup of the intermediate steps. The order of the reaction sequence is important as attempt to perform the lactamization after the oxidation of the 3-amino indole **39** led only to the degradation. Furthermore, it was found that Pd/C acted also as a catalyst to accelerate the peroxidation of **40** to **41**.[30,31] In its absence, the same reaction took several days to completion (see Supporting Information Figures S1 and S2).

For the total synthesis of leuconoxine skeleton from the same diketone (*R*)-**17**, we need to orient the nucleophilic addition of N4 to the iminyl carbon C21 instead of the carbonyl carbon C7 in the hypothetic intermediate **38** or its synthetic equivalents. To reach this goal, we thought to proceed by (a) reducing the nucleophilicity of the C4 nitrogen by converting the C4 primary amine to acetamide, inhibiting therefore its spontaneous condensation with the C7 carbonyl group; (b) enhancing the electrophilicity of the C21 iminyl carbon by its conversion to *N*-acyliminium taking advantage of the pendant ester function. While searching for conditions for this individual step, we aimed at finding simple protocols that are easily integrated into a one-pot process.

Conversion of (*R*)-diketone **17** to [6,5,6,6]spirotetracycle of scholarisine G is depicted in Scheme 5. Hydrogenation of (*R*)-**17** (Pd/C, EtOH) in the presence of acetic anhydride (5.0 equiv) afforded indolin-3-one **42** involving a sequence of (a) reduction of both nitro and azido groups; (b) selective condensation of the aniline nitrogen with the C21 ketone and the reduction of the resulting imine function; and (c) selective *N*-acetylation of the C4-primary amine. Without isolation, compound **42** was spontaneously oxidized to the unstable indol-3-one **43** upon purging the reaction mixture with argon followed by oxygen. Addition of potassium hydroxide into the above reaction mixture triggered the lactamization leading to δ-lactam *N*-acyliminium that was in situ trapped by ethanol to afford 2-ethoxyindolin-3-one **44** as a mixture of two

DOI: 10.1021/jacs.5b03619
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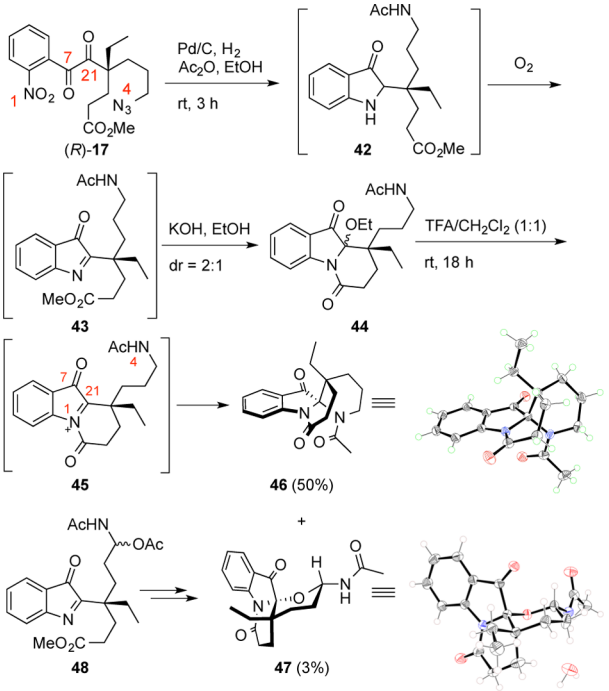
Scheme 5. Divert the Cyclization Manifold: From (*R*)-Diketone 17 to [6,5,6,6] Spiro-tetracyclic Skeleton 46

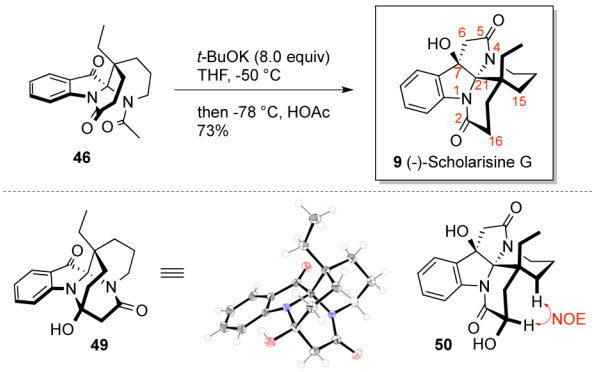


diastereomers (dr = 2:1). The lack of diastereoselectivity in this hemiaminal formation is of no consequence since it will be converted back to *N*-acyliminium ion in the next step. To our delight, treatment of the crude mixture of **44** with TFA in CH_2Cl_2 afforded the desired [6,5,6,6] spiro tetracycle **46** as an only diastereomer whose structure was fully determined by X-ray analysis. The intramolecular nucleophilic addition of amide NH to the in situ generated *N*-acyliminium ion **45** took place therefore from the side opposite to the neighboring ethyl group. We emphasize that the in situ acetylation of the primary amine N4 during hydrogenation was not a redundant step since it introduced the missing C2 unit needed for the synthesis of leuconoxine skeleton.

A side product **47** having a pyran ring was isolated in 3% yield from the reaction mixture in some experiments. Only one diastereomer was isolated and the structure was confirmed by X-ray analysis. Different from **46** in which the piperidine ring adopted a boat conformation, the pyran ring in **47** took a chair conformation with the C3 acetamido group at the equatorial position. A reasonable precursor to **47** would be hemiaminal **48**, which in turn was formed by palladium-catalyzed α-acetoxylation of the azide **17**. We believe that controlled conversion of alkyl azides to hemiaminals is a synthetically very useful transformation since they could serve as a latent *N*-acyliminium equivalent.[42a,48] Note that there are only very few methods allowing the generation of *N*-acylimines from aliphatic aldehydes.[49]

An intramolecular aldolization of **46** completed the synthesis of (−)-scholarisine G (**9**, Scheme 6). After extensive experimentations, it was found that (−)-scholarisine G (**9**) could be obtained in 73% yield by treatment of **46** with an excess amount of *t*-BuOK (8.0 equiv) at −50 °C, followed by quenching the reaction with acetic acid at −78 °C. The presence of an excess amount of base was crucial for the success of the reaction as the desired product could be detected only after 6 equiv of *t*-BuOK was added. Furthermore, quenching

Scheme 6. Total Synthesis of (−)-Scholarisine G (9)



the reaction with acetic acid at low temperature was also important as significant degradation was observed when the reaction was quenched with H_2O, MeOH or sat. aq. NH_4Cl. The structure of our synthetic compound was unequivocally confirmed by single crystal X-ray analysis. Consequently, our synthesis also confirmed the absolute configuration of (−)-scholarisine G (**9**), previously assigned based on the biosynthetic hypothesis.

A hemiaminal byproduct **49** resulting from the attack of enolate at the C2 amide carbonyl group rather than the C7 ketone group was isolated in around 1% yield. The carbinol structure **49** was unambiguously determined by X-ray analysis, representing one of the rare examples of stable tetrahedral intermediates resulting from the nucleophilic addition to amide carbonyl function.[14,50] We note here that the C2 amide carbonyl in **46** could in fact be considered as a vinylogous imide,[51] while the C7 ketone could be regarded as a vinylogous amide; therefore, the reactivity difference between the two carbonyl groups is not very pronounced.

It is also interesting to note that 16β-hydroxy-scholarisine G (**50**) was isolated in around 5% yield when an excess of LiHMDS was used as a base. The formation of **50** could be explained by oxidation of the in situ generated C16-enolate of **9** by adventurous air introduced during the TLC monitoring of the reaction. The absolute configuration of C16 was determined to be *R* based on the analysis of the coupling constant of H16 [δ 4.48 (dd, J = 6.8, 11.6 Hz)], and the NOE correlation between H16 and H15.

Scholarisine G and other leuconodines share an unusaual [5.5.6.6]diazafenestrane system that is extremely rare in nature.[52] Detailed analysis of X-ray structure of scholarisine G (**9**) indicated that the central carbon atom of the fenestrane is not particularly distorted. On the other hand, the bond length of N1−C2 (1.373 Å) is longer than that of N4−C5 (1.352 Å), while the pyramidalization angle of N1 (χ = −32) is larger than that of N4 (χ = −19.9).[53] In the ^{13}C NMR spectrum of **9**, it was observed that the C2 carbon had a resonance at a lower field (δ 173.6) than that of C5 (δ 170.0). All these data indicated that the delocalization of N1 lone pair electron to C2 carbonyl is less important than that of N4 to C5. Consequently, the C2 carbonyl carbon is more electrophilic than C5 and the C2 carbonyl oxygen is less nucleophilic than the C5 carbonyl oxygen. In line with this analysis, all our attempts to reduce scholarisine G with different hydride reducing agent afforded only the C2 carbonyl reduced product (see Supporting Information).[14] However, Dai and co-workers have reported an elegant solution to this selectivity problem by taking advantage of the higher nucleophilicity of the C5 carbonyl

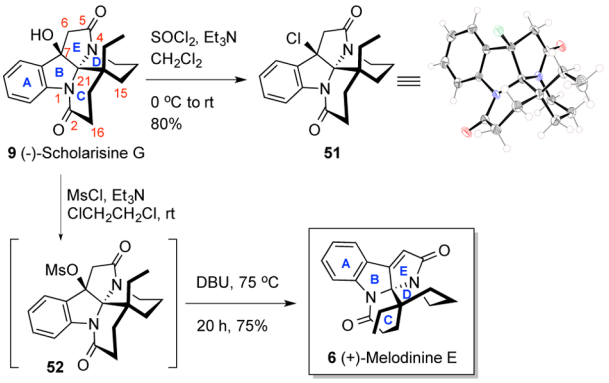
DOI: 10.1021/jacs.5b03619
J. Am. Chem. Soc. 2015, 137, 6712−6724

oxygen. Thus, γ-lactam in leuconoxine (**10**) was selectively converted to the methyl amidinium salt that was subsequently reduced by sodium cyanoborohydride to leuconodine D (**15**).[24]

(±)-Scholarisine G was also synthesized following the same synthetic route. While there are small discrepancies in the ^{1}H NMR spectrum between synthetic and natural (−)-scholarisine G (**9**), the synthetic (±)-scholarisine G (**9**) did not match that of the natural product. Both Tokuyama and Dai also noted that the ^{1}H NMR spectra of their synthetic (±)-scholarisine G did not match that of our synthetic (−)-scholarisine G. By detailed NMR titration experiments and analysis of the single crystal structures of both (±)- and (−)-scholarisine G, we demonstrated that scholarisine G showed interesting self-induced diastereomeric anisochronism (SIDA) phenomenon (vide infra).

The synthesis of (+)-melodinine E (**6**) from (−)-scholarisine G (**9**) is shown in Scheme 7. Treatment of a dichloromethane

Scheme 7. Transformation of (−)-Scholarisine G (9) to (+)-Melodinine E (6)



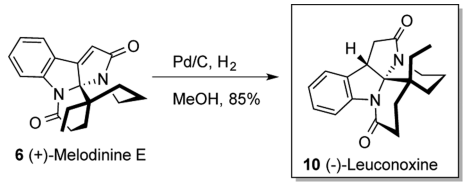
solution of **9** with thionyl chloride and triethylamine afforded the chlorinated product **51** in 80% yield whose structure was confirmed by X-ray diffraction analysis. Although base-promoted elimination of chloride in **51** did give **6**, the reaction was not very efficient in our hands. Alternatively, O-mesylation of the tertiary hydroxy group in **9** followed by a DBU-promoted elimination of the resulting mesylate afforded (+)-melodinine E (**6**) in 75% isolated yield.

In solid state, the D ring (piperidine) of fenestrane motif of melodinine E adopts a twisted boat conformation,[14] rendering it more strained and less stable relative to scholarisine G whose D ring is in a chair form. Indeed, while scholarisine G (**9**) was stable in a TFA/CH_2Cl_2 (v/v = 1/1) solution for several days, severe degradation occurred within 12 h when melodinine E (**6**) was dissolved in the same solvent. It is reasonable to assume that degradation of **6** went through the *N*-acyl iminium ion **7** (cf. Scheme 1) and that this intermediate might be easy to form from melodinine E under mild acidic conditions. This mechanistic assumption has very important bearing in our subsequent experimental design aimed at converting melodine E to other leuconodine congeners.

Postcyclization Phase: Bioinspired Diversification of (+)-Melodinine E (6). (+)-Melodinine E (**6**) was proposed to be the biosynthetic precursor of all the other leuconoxine group alkaloids with different oxidation states. With this idea in mind, we set out to explore these transformations in laboratory settings.

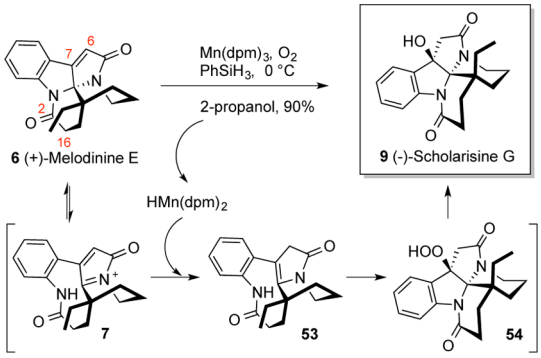
The transformation of (+)-melodinine E (**6**) to (−)-leuconoxine (**10**) was straightforward. Hydrogenation of **6** in the presence of catalytic amount of Pd/C in methanol gave (−)-leuconoxine (**10**) in 85% yield (Scheme 8).

Scheme 8. Postcyclization Phase: From (+)-Melodinine E (6) to (−)-Leuconoxine (10)



Selective hydroxylation of leuconoxine (**10**) at C6 position is difficult to realize due to the easy enolization of the C2 amide function as we stated earlier. Indeed, Kam and co-workers have shown that treatment of leuconoxine (**10**) with LDA followed by oxygen afforded 16-hydroxyleuconoxine as an only isolable product in 21% yield together with the recovered starting material.[14] Therefore, we thought that melodinine E could be an appropriate precursor for the synthesis of leuconodine A (**11**). A chemoselective 1,4-reduction of α,β-unsaturated amide in **6** would generate regioselectively the C6-enolate or its radical equivalent that could subsequently be oxidized to the leuconodine A (**11**). After many unsuccessful trials, we found that treatment of **6** with $Mn(dpm)_3$ and $PhSiH_3$ under O_2 atmosphere[54] afforded cleanly a single product whose structure was determined to be the (−)-scholarisine G (**9**) in 90% yield (Scheme 9). The result is at the first glance unexpected since

Scheme 9. Postcyclization Phase: Unexpected Conversion of (+)-Melodinine E (6) to (−)-Scholarisine G (9)



α,β-unsaturated amides are known to be transformed regioselectively to α-hydroxy amide under Mukaiyama conditions.[55] A possible explanation to the unexpected regioselectivity is the lability of the central aminal function. Under Mukaiyama conditions, melodinine E (**6**) may be in equilibrium with the *N*-acyliminium **7**, which could then be reduced to enamide **53** by the in situ generated Mn hydride species.[56] Trapping of the enamide **53** by Mn-peroxide or by molecular oxygen would afford the peroxide **54** that was subsequently reduced to scholarisine G (**9**). Alternatively, direct hydride transfer from $HMn(dpm)_2$ to the C6 position in an S_N2' manner could also account for the formation of enamide **53**.

On the basis of above experiment observation and mechanistic hypothesis, an unusual α-hydroxylation of the

DOI: 10.1021/jacs.5b03619
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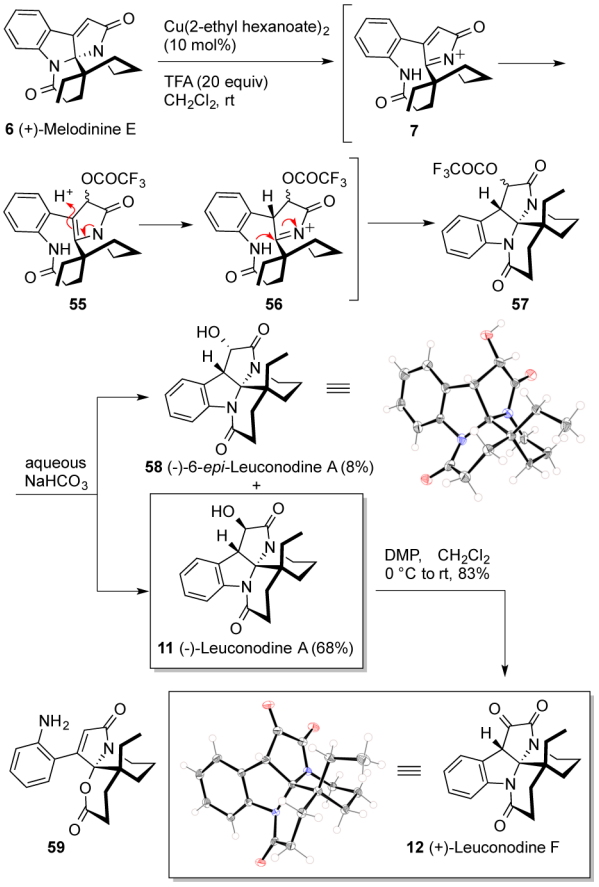
α,β-unsaturated amide in **6** was finally developed (Scheme 10). Treatment of a CH_2Cl_2 solution of **6** with 20 equiv of TFA in

Scheme 10. Postcyclization Phase: From (+)-Melodinine E (6) to (−)-Leuconodine A (11) and (+)-Leuconodine F (12)

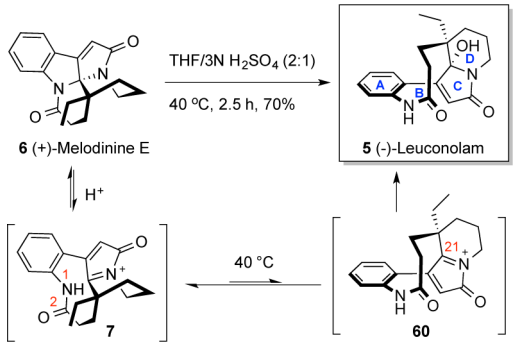


the presence of a catalytic amount of copper(II) 2-ethylhexanoate (0.1 equiv) gave an unstable trifluoroacetate **57** as a mixture of two diastereomers. Without purification, the reaction mixture was worked up with aqueous $NaHCO_3$ to directly provide (−)-leuconodine A (**11**) in 68% yield, together with 8% of 6-*epi*-leuconodine A (**58**). Both structures were unambiguously confirmed by X-ray analysis. We hypothesized that the reaction might go through the *N*-acyliminium intermediate **7**. Conjugate addition of trifluoroacetate to *N*-acyliminium **7** would afford enamide **55**, which, upon protonation, would provide the *N*-acyl iminium salt **56**. Transannular cyclization of **56** would then furnish **57**, which, upon aqueous workup, afforded two separable diastereomers **11** and **58**. When copper(II) triflate (0.1 equiv) was used as a catalyst, the aniline **59**[14] was isolated in 15% yield in addition to **11** and **58**. By increasing the loading of $Cu(OTf)_2$ (0.6 equiv), the yield of **59** was increased to 70%. We assumed that $Cu(OTf)_2$, due to its increased Lewis acidity, might be able to activate the six-membered lactam leading therefore to its hydrolysis. A control experiment showed that in the absence of copper salt, heating a TFA solution to 70 °C also led to the formation of **11** and **58**, albeit in a much lower yield.

Oxidation of (−)-leuconodine A (**11**) by DMP afforded (+)-leuconodine F (**12**) in 83% yield.[14] The structure of the synthetic leuconodine F (**12**) was confirmed by X-ray structural analysis.

(−)-Leuconolam (**5**) was proposed to be the biogenetic precursor of melodinine E (**6**), and biomimetic transformation of **5** to **6** under acidic conditions has been realized in laboratory settings.[10a,b,14] We have reversed the process by converting (+)-melodinine E (**6**) to (−)-leuconolam (**5**) as shown in Scheme 11. Treatment of a solution of **6** in THF/3 N H_2SO_4

Scheme 11. Postcyclization Phase: From (+)-Melodinine E (6) to (−)-Leuconolam (5)



(v/v = 2/1) at 40 °C for 2.5 h afforded (−)-leuconolam (**5**) in 70% isolated yield. It was noted that the starting material disappeared rapidly under acidic conditions at room temperature leading to the presumed *N*-acyl iminium ion **7**. However, only melodinine E was recovered upon workup indicating that the transannular cyclization of **7** back to **6** is a kinetically favored process. To promote the formation of leuconolam, heating the reaction mixture is the key. We assumed that, upon heating to 40 °C, the rotation of C1−N2 bond took place to convert the *trans* C1−N2 amide bond to the higher energy *cis*-isomer as found in **60**. The intramolecular aminal formation was impossible in **60** due to the geometric constraint as the nucleophilic N1 atom is too far away from electrophilic C21 iminium carbon; the intermolecular addition of water to C21 became therefore competitive leading to the formation of leuconolam (**5**). The structure of our synthetic leuconolam was unambiguously confirmed by X-ray structural analysis. It is worth noting that the addition of water to C21 of the *N*-acyliminium took place from the same face occupied by the neighboring ethyl substituent placing therefore both the hydroxy and the ethyl groups in the convex face defined by the B−C−D ring. Additionally, an axial chirality was created in this transformation and only one atropisomer corresponding to the natural product was produced.

Direct aromatic hydroxylation of (−)-leuconoxine (**10**) at C10 would convert **10** to (−)-leuconodine C (**13**). However, all our attempts toward this end were unsuccessful. We then thought that it should also be possible to take advantage of the equilibrium between (+)-melodinine E (**6**) and the *N*-acyl iminium ion intermediate **7** to introduce a hydroxy group into the C10 position. Our working hypothesis exploiting the transiently generated secondary amide function is as follows (Scheme 12). Reaction of the secondary amide function in **7** with a hypervalent iodine reagent could afford **61** in which the aromatic C10 position was now susceptible to nucleophilic attack to furnish **62**. Rearomatization of **62** followed by tansannular aminal formation would afford the desired 10-hydroxy derivative (e.g., **63**).[57] While conceptually interesting, the potential complication was the high electrophilicity of the C6 position of the intermediate **7**, and we have in fact exploited

DOI: 10.1021/jacs.5b03619
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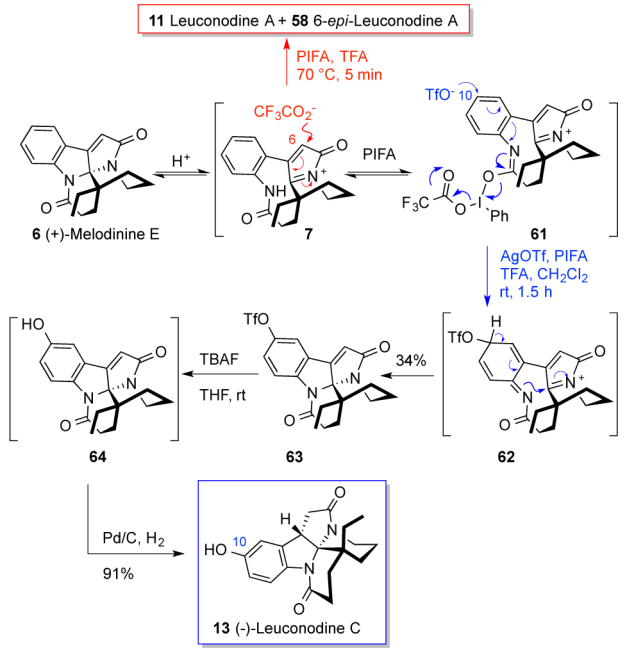
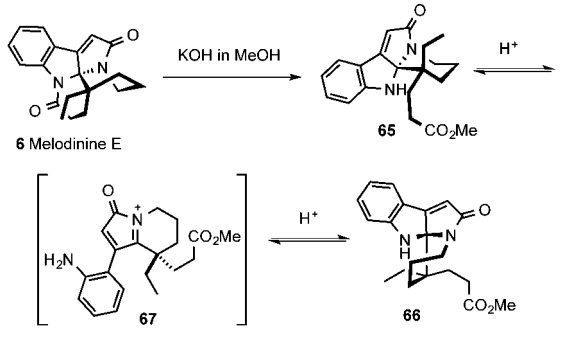
Scheme 12. Postcyclization Phase: From (+)-Melodinine E (6) to (−)-Leuconodine C (13)



this latter property for converting melodinine E (**6**) to leuconodine A (**11**, cf. Scheme 10). Indeed, preliminary experiments using PIFA as an oxidant in neat TFA afforded, after basic workup, only leuconodine A (**11**) and its C6-epimer **58**, resulting from the hydroxylation at the C6 postion.[57b] The ratio and yields of **11** and **58** were similar to those obtained using copper(II) 2-ethyl hexanoate as a catalyst. After many trials, we were finally able to obtain the desired 10-OTf melodinine E (**63**) in 34% yield by treatment of a dichloromethane solution of **6** in the presence of AgOTf (2.5 equiv), PIFA (1.5 equiv) and TFA (20 equiv) at room temperature for 1.5 h. Hydrolysis of the sulfonate (TBAF, rt) afforded phenol **64** cleanly,[58] which was unstable and underwent degradation upon aqueous workup. Therefore, hydrogenation was performed directly by adding Pd/C to the above reaction mixture to afford (−)-leuconodine C (**13**) in 91% overall yield.

Postcyclization Phase: Conversion of (+)-Melodinine E (6) to Other Non-Natural Polycyclic Compounds. (+)-Arboloscine (**14**) was the ring-opened form of (+)-melodinine E (**6**). Selective methanolysis of **6** could in principle provide a direct access to **14** (Scheme 13). However, treatment

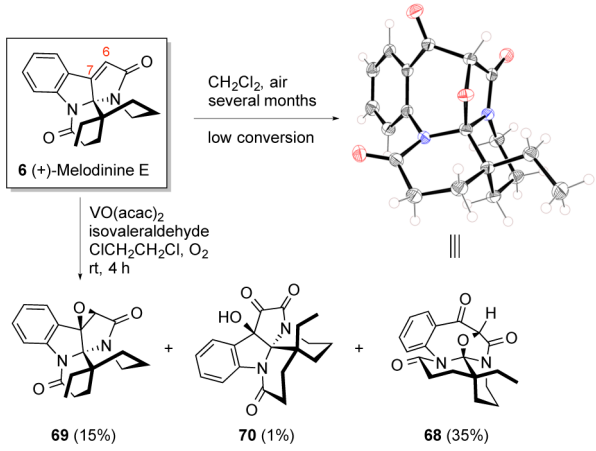
Scheme 13. Base-Promoted Methanolysis of Melodinine E (6) to Tetracycle 65



of **6** with KOH in MeOH afforded the methyl ester **65** resulting from the selective ring opening of the δ-lactam. We noted that the aminal function in **65** was unstable and its stereogenic center is readily epimerized even under mild acidic conditions ($CDCl_3$). The equilibrium between **65** and **66** went through most probably the *N*-acyl iminium intermediate **67**.

We have accidentally found that keeping a CH_2Cl_2 solution of **6** for several months resulted in the formation of a complex oxa-bridged polycycle **68**, albeit in a very low conversion (Scheme 14). The structure of **68** was initially proposed based on detailed NMR studies and was later confirmed by X-ray analysis.

Scheme 14. Postcyclization Phase: From (+)-Melodinine E (6) to an Oxabridged Polycycle



The X-ray structure of melodinine E (**6**) showed that the C6−C7 double bond, especially C7 showed similar character as that of the strained bridgehead double bond. For example, the value of pyramidalization angle (χ = 30.5°) of C7 is between that of the bridgehead carbon of strained double bond in [3,3,1] (χ = 39.0°, τ = 10.8°) and [4,3,1] (χ = 22.7°, τ = 6.4°) bicyclic systems, while the torsion angle (τ = 21.0°) is larger. Therefore, we thought that the formation of **68** might be initiated by the oxidation of the C6═C7 double bond since the ground-state triplet oxygen is known to oxidize the angle-strained olefins in a concentration-depending manner.[59] However, an attempt to increase the efficiency of this transformation by performing the reaction at high concentration (*c* 1.0 M) was unsuccessful.

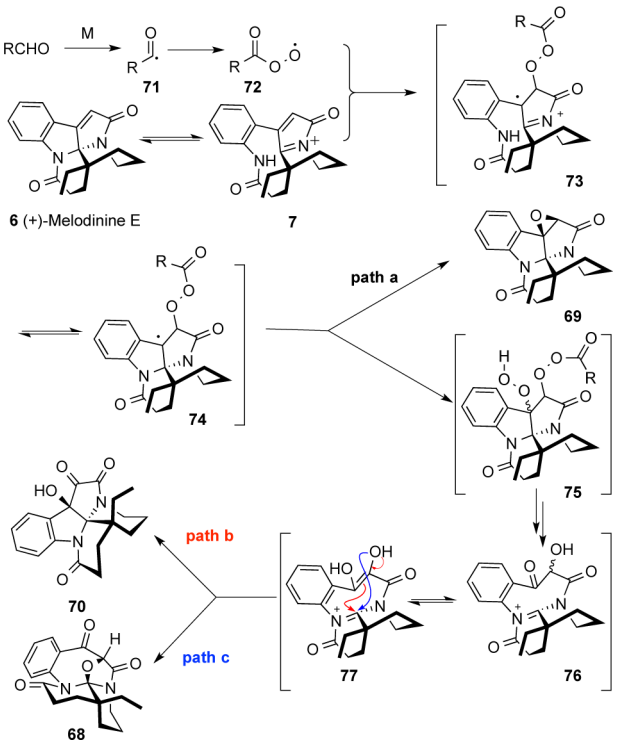
Intrigued by the molecular structure of **68** and its easy formation under aerobic conditions from melodinine E (**6**), we thought that such compound, yet unknown, could also exist in nature. Therefore, we screened different oxidative conditions in order to increase the efficiency of this transformation. Interestingly, Mukaiyama epoxidation using molecular oxygen as a terminal oxidant turned out to be the most effective. Simply stirring a dichloroethane solution of **6** and an excess of isovaleraldehyde in the presence of a catalytic amount of $VO(acac)_2$ under oxygen atmosphere[60] afforded **68** in 35% yield. Epoxide **69** and 7-hydroxy-leuconodine F (**70**) were also isolated in yields of 15% and 1%, respectively.

Resubmitting the epoxide **69** to the Mukaiyama epoxidation conditions resulted in the full recovery of the starting material. The result of this control experiment indicated therefore that epoxide **69** is not the intermediate on the way to **68** and **70**. A possible reaction pathway accounting for the oxidation of

DOI: 10.1021/jacs.5b03619
J. Am. Chem. Soc. 2015, 137, 6712−6724

melodinine E (**6**) to all the three products is depicted in Scheme 15. Metal mediated oxidation of aldehyde afforded acyl radical **71**, which was trapped by molecular oxygen to give acylperoxy radical **72**.[61] While **72** could in principle add to C7, a β position of the α,β-unsaturated amide unit in **6**, we hypothesized that this may not take place in accordance with our previous experimental observations. The acylperoxy radical **72** would instead add to C6 of the in situ generated *N*-acyliminium ion **7** to produce the acylperoxide intermediate **73**, which is in equilibrium with the cyclic aminal **74**. An intramolecular radical trapping by the acyl peroxide could give the epoxide **69** (path a). On the other hand, further oxidation of **74** would afford intermediate **75**, which underwent Grob type fragmentation to give *N*-acyl iminium ion intermediate **76**. The α-hydroxy ketone in **76** was in equilibrium with its enol form 77. Cyclization via C−C bond (path b) formation or via C−O bond (path c) formation would then give **70** or **68**, respectively.

Scheme 15. Proposed Mechanism for the Oxidation of (+)-Melodinine E (6) to 68, 69, and 70



In light of the easy formation of **68** under biomimetic oxidative conditions, we would not be surprised if this compound would be isolated one day from the natural sources.

Self-Induced Diastereomeric Anisochronism (SIDA) Phenomenon in ^{1}H NMR Spectra of Scholarisine G (9) and Leuconodines A (11) and C (13). It is now well-known that enantiomers and racemates could show different physical and chemical properties because of the interactions between different enantiomers, thus resulting in the nonlinear effects in asymmetric synthesis,[62] and the phenomenon of self-disproportionation of enantiomers (SDE).[63] The self-induced diastereomeric anisochronism (SIDA) phenomenon refers to the fact that in some cases, enantiomers and racemic mixtures show different NMR spectra in achiral solvents, and distinct signals of each enantiomer could be obtained.[64−71,72a] The extent of spectroscopic difference is concentration- and solvent-dependent indicating an autoassociation phenomenon. However, the SIDA phenomenon is still overlooked nowadays by many practitioners of organic synthesis for several reasons. First, there were only limited examples of SIDA phenomenon reported since its first disclosure in 1969 by Williams and co-workers on the nonequivalence of the ^{1}H NMR spectra of racemic and enantiopure dihydroquinine.[64a] In addition, different terms such as solute−solute interactions of enantiomers,[64a] self-induced anisochrony (SIA),[65] statistically controlled associate diastereoisomerism (SCAD)[66] self-induced diastereomeric anisochronism,[67] self-induced nonequivalence,[68] and self-discrimination of the enantiomers[69] have been

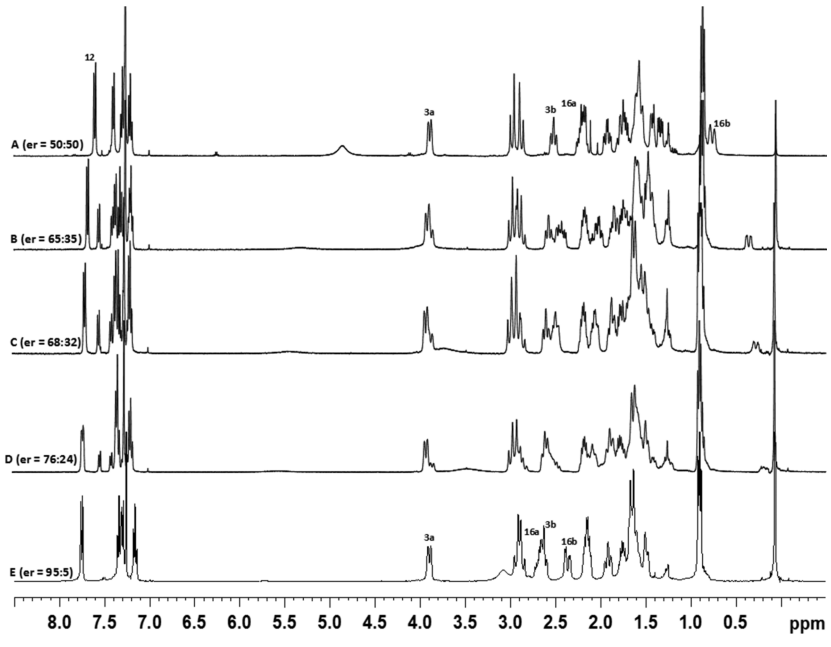


Figure 1. ^{1}H NMR spectra of scholarisine G (**9**) with different enantio-purities in $CDCl_3$.

DOI: 10.1021/jacs.5b03619
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proposed to explain the same phenomenon that might complicate the situation. Second, the differences in NMR spectra between enantiomers and racemates were so small in most of the cases that they were arbitrarily considered as "identical". Third, in natural product research, it is often difficult to obtain both enantiomers and racemates for comparison. Indeed nowadays, synthetic chemists tend to directly investigate the enantioselective approaches without caring too much about the racemic version. To the best of our knowledge, only two natural products, dihydroquinine[64a] and spirobrassinin,[64p] were reported to show SIDA phenomenon.

The NMR spectra of our synthetic (−)-scholarisine G (ee 90%) matched with the natural product, although small discrepancies still exist (Figure 1E). However, several tiny "impurity" signals were always found in the spectra of our synthetic (−)-scholarisine G, and the amount of which varied with the concentration. The "impurity" signals disappeared and only one set of signals corresponding to (−)-scholarisine G was found when CD_3OD was added.[73] On the other hand, the ^1H NMR spectrum of (±)-scholarisine G in $CDCl_3$ (Figure 1A) was not identical to that of (−)-scholarisine G (Figure 1E), especially the chemical shift of H16. While two H16 protons of (−)-scholarisine G appeared normally having chemical shifts of 2.65 and 2.35 ppm, respectively, one of the H16 protons of the racemic scholarisine G resonanced at abnormally high field (δ = 0.80 ppm) as it was positioned beneath an electron rich aromatic ring. Interestingly, the ^1H NMR spectrum shifted significantly when CD_3OD was added to the $CDCl_3$ solution of (±)-scholarisine G (see Supporting Information Figure S3). The ^1H NMR spectrum became similar to that reported for (−)-scholarisine G when the ^1H NMR was recorded in a 2.7/1 (v/v) mixture of $CDCl_3/CD_3OD$.

The aforementioned observation seems to indicate that hydrogen bond played a key role in the abnormal behavior of the NMR spectra of scholarisine G and the SIDA could be responsible for the observed NMR spectra differences between the (−)- and (±)-scholarisine G. To further confirm the presence of SIDA phenomenon, scholarisine G with different enantiomeric purities were prepared by titration of (−)-scholarisine G with (±)-scholarisine G and their ^1H NMR spectra were recorded. Some of these spectra are displayed in Figure 1 (see Supporting Information Figure S4 for additional spectra). As expected, both (±)- and (−)-scholarisine G showed only one set of signals (Figure 1A and 1E), which were different from each other. Two sets of peaks, corresponding to each enantiomer, were found for nonracemic samples (Figure 1B-1D), and the enantiomeric ratio could be read out directly by measuring the ratio of the corresponding integrals. Furthermore, when a concentrated solution of nonracemic sample of scholarisine G in $CDCl_3$ was diluted, the two distinct sets of peaks started to collapse, and the spectrum became similar to that of (−)-scholarisine G at high dilution (see Supporting Information Figure S5).

Supramolecular self-association between enantiomers in solution is generally responsible for the SIDA. Although $\pi-\pi$ stacking can induce SIDA,[70] hydrogen bonding-induced dimerizaiton/oligomerization is more frequently associated with this phenomenon. While mathematic models[71] and computational studies[74] have been published to account for the SIDA phenomenon. X-ray structures of both racemic and enantiopure SIDA molecules have, to the best of our knowledge, never been obtained in order to understand the phenomenon at molecular level.[72] Fortunately enough, we were able to grow single crystals of both (±)- and (−)-scholarisine G suitable for X-ray diffraction analysis. In the solid state of (±)-scholarisine G (Figure 2a, space group $P\bar{1}$), heterodimer

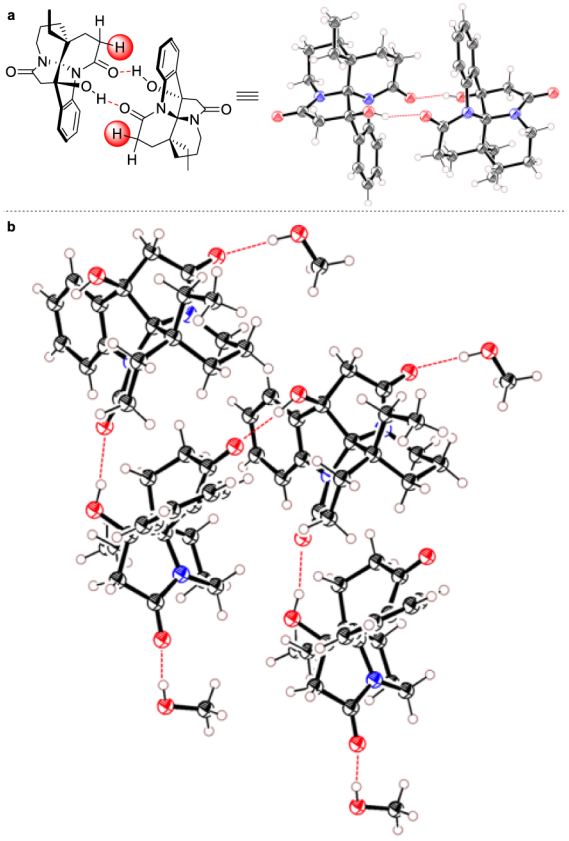

Figure 2. (a) X-ray structure of (±)-scholarisine G (**9**). (b) X-ray structure of (−)-scholarisine G (**9**).

was formed by two hydrogen bonds between C2 carbonyl group of one enantiomer and C7 hydroxy group of its antipode, forming a 14-membered ring. In this dimeric structure, two ethyl substituents pointed toward two different directions avoiding therefore the steric repulsion. On the other hand, the crystal structure of (−)-scholarisine G (space group $P2_12_12_1$) appeared as a helix by the iteratively formed hydrogen bonds between C2 carbonyl group of one molecule and C7 hydroxy group of the other having the same absolute configuration. In addition, one molecule of methanol formed an additional hydrogen bond with C5 carbonyl group at the outer sphere of the helix.

Although the structural information obtained from the solid state could not be directly transposed into solution structure, we found that the high field shift of H16 observed in the ^1H NMR spectra of (±)-scholarisine G in $CDCl_3$ was consistent with its crystalline heterodimeric structure, in which one of the H16 protons was located at the shielding area of the phenyl ring of the other enantiomer. Thus, we believed that the heterodimer of (±)-scholarisine G formed via hydrogen bond was the major species responsible for the SIDA phenomenon, which could be broken down to monomer upon addition of CD_3OD or by dilution

Two other natural products, leuconodines A and C having a hydroxy group at C6 and C10, respectively, also displayed the SIDA phenomenon, albeit with different magnitude (Supporting Information Figures S6, S8, and S9). In the cases of

DOI: 10.1021/jacs.5b03619
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scholarisine G (Supporting Information Figure S4) and leuconodine C (Supporting Information Figures S8 and S9), significantly different ^{1}H NMR spectra were obtained for racemates and enantiomers. However, only small discrepancy in the chemical shift of H6 was noticed in the ^{1}H NMR spectra of (±)- and (−)-leuconodine A (Supporting Information Figure S6), which could be easily considered as "identical" if no particular attention were paid (Supporting Information Figure S6). The presence of SIDA phenomenon of leuconodines A and C was also due to the H-bonding induced dimer formation as evidenced from the results of dilution experiments (Supporting Information Figures S7, S10, and S11) as well as the X-ray structural analysis of both the racemates (Figures 3 and 4) and the enantiomers (see Supporting Information). In (±)-leuconodine A, a 10-membered ring was formed via two H-bonds between two enantiomers (Figure 3a), while H-bond network in (−)-leuconodine A needs to be relayed by water molecules (Figure 3b). In the case of (±)-leuconodine C, an 18-membered H-bonded macrocycle was generated between two enantiomers (Figure 4). As it is evident from our studies, there is no direct correlation between the ring size of the H-bonding network and the magnitude in NMR spectra difference for these SIDA molecules. On the other hand, it was found that the SIDA phenomenon was configuration-dependent as no obvious differences were observed between racemates and enantiomers of *epi*-leuconodine A, probably because the formation of heterodimer was hindered in this case. Finally, no obvious differences between the racemates and enantiomers were observed in the NMR spectra of both leuconoxine and melodinine E lacking the hydroxy group. Obviously, dimer formation was impossible with these two alkaloids due to the lack of a H-bond donor (hydroxy group).

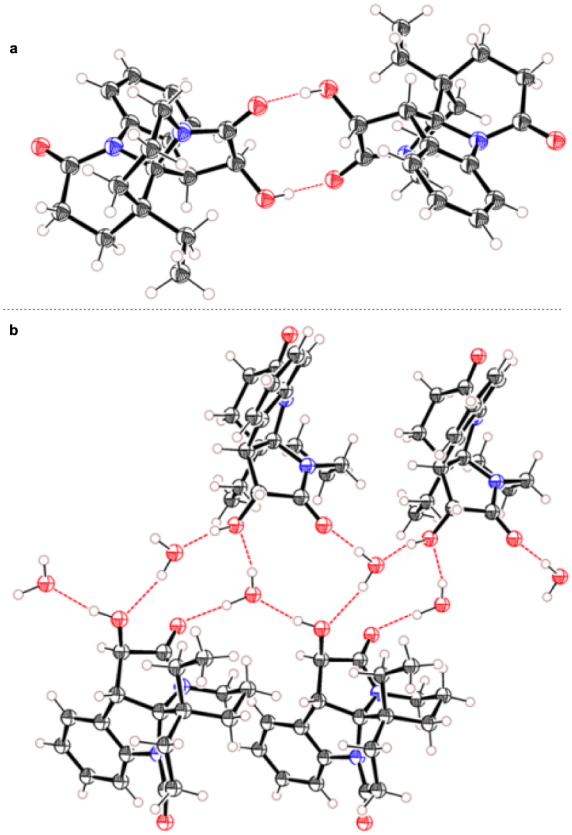

Figure 3. (a) X-ray structure of (±)-leuconodine A (**11**). (b) X-ray structure of (−)-leuconodine A (**11**).

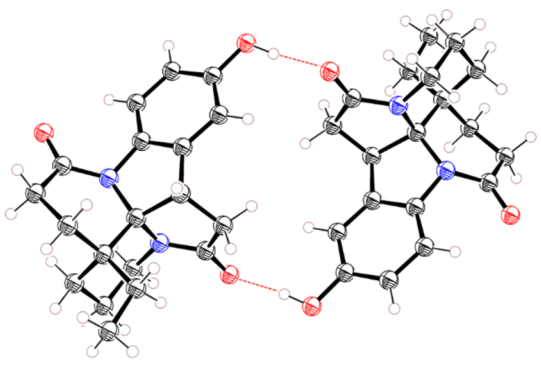

Figure 4. X-ray structure of (±)-leuconodine C (**13**).

CONCLUSION

In conclusion, we developed a unified strategy for the enantioselective synthesis of leuconolam-leuconoxine-mersicarpine subfamily of *Aspidosperma* alkaloids. A simple 2,6,6-trisubstituted cyclohexenone derivative (*S*)-**18**, readily accessible by the Suzuki−Miyaura cross-coupling reaction between enantiomerically enriched vinyl iodide (*S*)-**20** and 2-nitrophenyl boronic acid (**19**) served as a common intermediate for all the targeted natural products. Ozonolysis of (*S*)-**18** afforded stable diketo ester (*R*)-**17** that was subsequently converted to two skeletally different natural products, (−)-mersicarpine (**8**) and (−)-scholarisine G (**9**), respectively. Key to the success of the structure diversification is the fine-tuning of nucleophilicity of primary amine (N4) and the electrophilicity of C7 carbonyl vs C21 carbonyl/iminyl groups in the putative 3*H*-indol-3-one intermediate **38**. Dehydration of (−)-scholarisine G (**9**) afforded (+)-melodinine E (**6**) that was subsequently served as springboard to reach (−)-leuconoxine (**10**), (−)-leuconodine A (**11**), (−)-leuconodine C (**13**), (+)-leuconodine F (**12**), and (−)-leuconolam (**5**). The development of all these transformations was based on the chemical reactivity of the hypothetic *N*-acyliminium ion **7**, generated in situ from (+)-melodinine E (**6**). Indeed, the formation of this intermediate formally inversed the polarity of the C6═C7 double bond and at the same time, converted the tertiary amide to the secondary amide allowing therefore a traceless activation of the latter function. Fine-tuning the reaction conditions allowed us to introduce regio- and stereoselectively a hydroxy group to the C6, C7, C10, and C21 positions of melodinine E leading directly to the related natural products. A structurally unusual oxabridged oxadiazafenestrane **68** was formed by slow aerobic oxidation of melodinine E (**6**) and conditions were developed for a more efficient generation of this polycyclic compound. During the course of this study, the self-induced diastereomeric anisochronism (SIDA) phenomenon was observed for scholarisine G (**9**) and leuconodines A (**11**) and C (**13**). We obtained the X-ray structures of both racemic and enantiopure natural products. The crystal packing of these two forms nicely explained the chemical shift difference observed in the ^{1}H NMR spectra of racemic and enantiopure compounds in an achiral environment.

DOI: 10.1021/jacs.5b03619
J. Am. Chem. Soc. 2015, 137, 6712−6724

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectroscopic and crystallographic data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b03619.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank EPFL (Switzerland), the Swiss National Science Foundation (SNSF) and the Swiss National Centres of Competence in Research (NCCR) for financial support. We are grateful to Dr. Rosario Scopelliti for performing X-ray structural analysis.

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