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Unified Strategy to Monoterpene Indole Alkaloids: Total Syntheses of (±)-Goniomitine, (±)-1,2-Dehydroaspidospermidine, (±)-Aspidospermidine, (±)-Vincadifformine, and (±)-Kopsihainanine A

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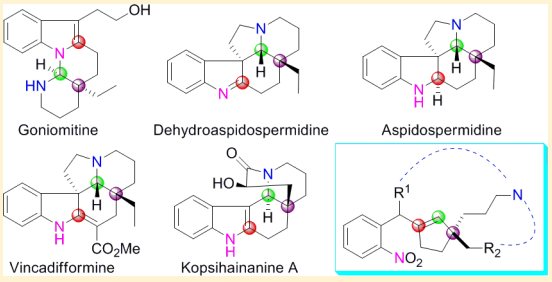
Supporting Information

ABSTRACT: Total syntheses of (±)-goniomitine, (±)-1,2-dehydroaspidospermidine, (±)-aspidospermidine, (±)-vincadifformine, and (±)-kopsihainanine A were achieved featuring two common key steps: (1) a palladium-catalyzed decarboxylative vinylation that provides quick access to cyclopentene intermediates containing all of the carbons present in the natural products and (2) an *integrated oxidation/reduction/cyclization* (*i*ORC) sequence for skeletal reorganization that converts the cyclopentenes to the pentacyclic structures of the natural products. By incorporation of a geometric constraint to *i*ORC substrates, both the chemoselectivity (C7 vs N1 cyclization) and the stereoselectivity (trans- vs cis-fused ring system) of the cyclization process can be controlled.



INTRODUCTION

The monoterpene indole alkaloids, in spite of their structural diversity,[1] are all biosynthetically derived from strictosidine (**1**), which is in turn obtained by the union of two building blocks: tryptamine (**2**) and secologanin (**3**) (Scheme 1a).[2] The simplicity and beauty of such an approach endorsed by nature are indeed striking. We recently initiated a research program aimed at mimicking nature's way of synthesis at the strategic level, namely, couple and divert, to reach skeletally diverse natural products from a common intermediate (Scheme 1b), and we chose *Aspidosperma* alkaloids **4**–**8** as our targets to evolve our synthetic strategy. Two additional guidelines directed our synthesis design: (a) to construct the indole unit at a late stage of the synthesis instead of using tryptamine or other indole-containing compounds as starting materials and (b) to construct the polycyclic ring system by a one-pot domino cyclization process. Toward this end, we thought that the functionalized cyclopentene derivative **9** could serve well as a springboard to reach topologically different structures by varying the nature of the substituents and their connectivity. Indeed, by a sequence of ozonolysis[3] and reduction of the latent amine functions, one could obtain a diamino dicarbonyl intermediate that could undergo subsequently controlled polycyclization to provide diverse skeletons of *Aspidosperma* alkaloids. While different multistep syntheses of **9** could be envisaged, the direct decarboxylative coupling of two readily accessible building blocks, the substituted potassium *o*-nitrophenylacetate **10** and vinyl triflate **11**, was deemed to be the method of choice. The selected targets shown in Scheme 1 represent three different skeletons of *Aspidosperma* alkaloids with different ring connectivity and stereochemistry. Therefore, in addition to accomplishing the total syntheses of these individual natural products, we aimed at addressing the following issues that could be of general interest in synthetic chemistry: (a) control of the chemoselectivity of the cyclization in order to obtain either goniomitine (**4**) or aspidospermidine skeletons (**5**–**7**); (b) control of the stereochemistry of the cyclization to produce either the cis-fused C/D ring (**5**–**7**) or trans-fused C/D ring (**8**). We report herein solutions to both issues through the development of concise syntheses of the aforementioned natural products.[4]

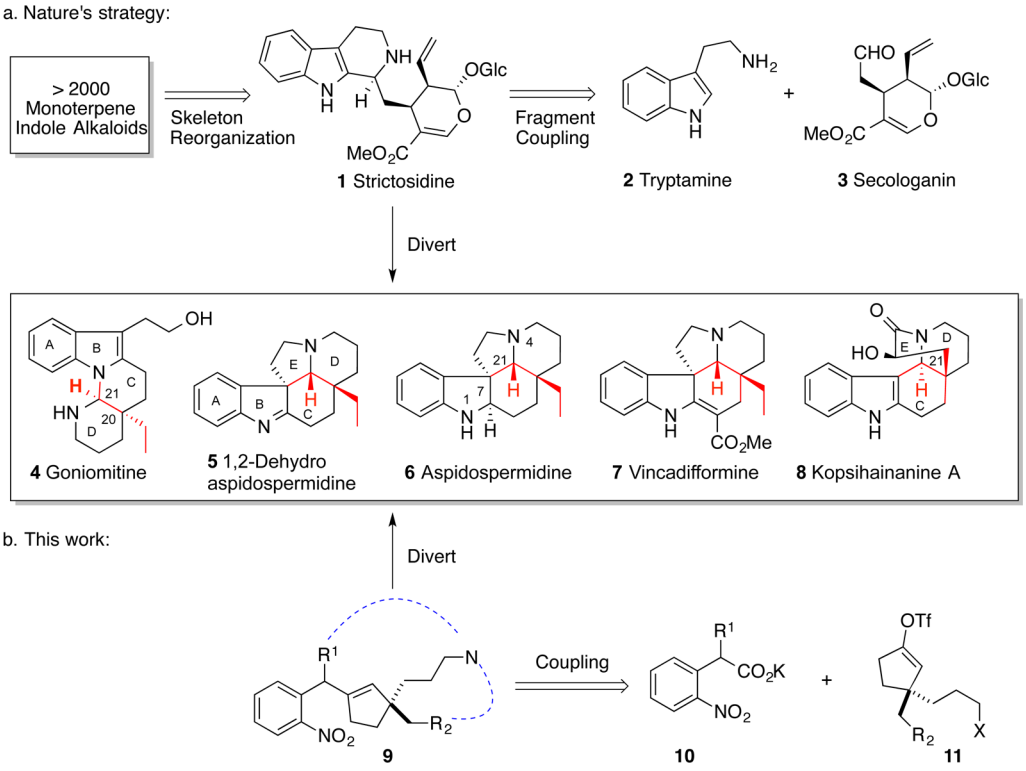
RESULTS AND DISCUSSION

Total Synthesis of Goniomitine (4). Goniomitine (**4**), a unique member of the *Aspidosperma* alkaloids family, was isolated from the root bark of *Gonioma malagasy* by Husson and co-workers in 1987.[5] The unprecedented octahydroindolo-[1,2-*a*][1,8]naphthyridine skeleton, together with a tryptophol moiety rather than the normal tryptamine fragment, results from the oxidative skeletal rearrangement of vincadifformine (**7**).[1,6] The interesting molecular architecture and potent antiproliferative activities[7] of this natural product have made it a popular synthetic target.[8] Construction of the 2,3-difunctionalized indole followed by stepwise formation of rings C and D is a common feature of these reported syntheses. The synthetic routes have nevertheless been significantly

Received: September 10, 2014

   dx.doi.org/10.1021/ja509329x | J. Am. Chem. Soc. XXXX, XXX, XXX–XXX

Scheme 1. Monoterpene Indole Alkaloid Synthesis: (a) Biogenesis and (b) Our Approach

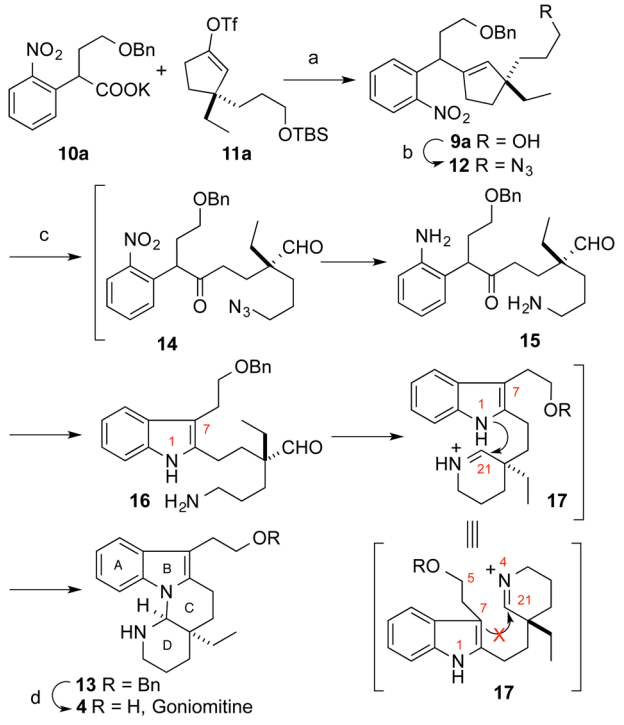


shortened since Takano's inaugural 28-step synthesis[8a] thanks to the development of new reactions/strategies.

Different from previous syntheses, we thought to build the whole tetracyclic scaffold of goniomitine from functionalized cyclopentene **12** (see Scheme 2) in one pot by an *i*ntegrated *o*xidation/*r*eduction/*c*yclization (*i*ORC) sequence. Compound **12** in turn was thought to be accessible by Pd-catalyzed decarboxylative coupling of **10a** with **11a**. Although intramolecular decarboxylative allylation/benzylation of nitrophenyl acetates[9] and intermolecular arylation of nitrophenyl acetates[10] are known, we noted at the outset of this work that vinyl triflates have never been employed as coupling partners in decarboxylative coupling with aliphatic carboxylic acids.[11,12] With potassium *o*-nitrophenylacetate and cyclohex-1-en-1-yl trifluoromethanesulfonate as test substrates, the conditions for the decarboxylative vinylation were surveyed by systematically varying the Pd source, ligand, solvent, and additives. The optimum conditions consisted of heating a solution of the two coupling components in DMF or diglyme (c = 0.2 M) at 100 °C in the presence of $[Pd(allyl)Cl]_2$ (2.0 mol %) and X-Phos (6.0 mol %). Under these conditions, the decarboxylative coupling products **9** were obtained in good to excellent yields.[4] Of importance to our total synthesis project is the observation that α-alkylated nitrophenyl acetates participated in the reaction to provide the cross-coupling products in good yields.

The total synthesis of goniomitine is summarized in Scheme 2.[4] The key Pd-catalyzed decarboxylative vinylation of potassium 4-(benzyloxy)-2-(2-nitrophenyl)butanoate (**10a**) using vinyl triflate **11a** occurred without event to afford, after in situ O-desilylation (TBAF), the coupling product **9a** in 70% yield as a mixture of two diastereomers (dr = 1/1). The presence of two diastereomers was of no consequence, as they displayed identical reactivity in the next synthetic operation that converted the benzylic stereogenic center to an achiral sp^2-hybridized carbon. Mitsunobu reaction[13] of alcohol **9a** with DPPA in the presence of DIAD and PPh_3 at room temperature

Scheme 2. Total Synthesis of (±)-Goniomitine (4)[a]



[a]Reagents and conditions: (a) $[Pd(allyl)Cl]_2$ (5.0 mol %), X-Phos (15.0 mol %), diglyme, 100 °C, 2 h; TBAF, rt, 4 h, 70%. (b) DPPA, DIAD, Ph_3P, THF, 0 °C to rt, 3 h, 72%. (c) O_3, $NaHCO_3$, MeOH, −78 °C; Me_2S, −78 °C to rt; Zn, $CaCl_2$, reflux, 2 h, 80%. (d) Sodium naphthalenide, THF, −20 °C, 15 min, 65%.

dx.doi.org/10.1021/ja509329x | J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

(rt) afforded azido compound **12** in 72% yield. The one-pot *i*ORC process was realized as follows. Ozonolysis of **12** in methanol at −78 °C in the presence of $NaHCO_3$[14] followed by the addition of dimethyl sulfide (−78 °C, then at rt for 24 h) and then activated zinc and $CaCl_2$ and heating of the reaction mixture to reflux furnished **13** in 80% yield as the only diastereomer. The presence of $CaCl_2$ was crucial for the success of the reaction, as other additives such as NH_4Cl or AcOH significantly decreased the yield of **13**.[15] On the other hand, attempts to reduce the ozonide directly after ozonolysis under the same conditions ($Zn/CaCl_2$) resulted in complete decomposition. The 1,5-dicarbonyl compound **14** formed after the ozonolysis step[16] was isolable, and it was fully characterized. Upon concomitant reduction of the nitro and azido groups, diamino dicarbonyl intermediate **15** cyclized spontaneously in a chemo- and regioselective manner to afford **17** via intermediate **16**. Intramolecular attack of the indolyl nitrogen (N1) on the iminium from the face opposite to the ethyl substituent would diastereoselectively produce the cis-fused C/D ring system, thus completing the construction of tetracycle **13**. In this operationally simple process, oxidative scission of a double bond, chemoselective reduction of the azido and nitro groups without touching the ketone, the aldehyde, the iminium intermediate, or the final aminal function, and formation of three C−N bonds with concurrent formation of three rings took place with a high degree of chemo-, regio-, and diastereoselectivity.[17] The sequence completely reorganized the skeleton of the starting material, allowing the conversion of an easily accessible cyclopentene derivative to the tetracyclic structure of goniomitine. Finally, deprotection of the benzyl ether in the presence of the sensitive aminal group was best realized with sodium naphthalenide[18] to give (±)-goniomitine (**4**) in 65% yield. The spectroscopic data for the synthetic goniomitine were identical to those reported in the literature.

Total Syntheses of 1,2-Dehydroaspidospermidine (5), Aspidospermidine (6), and Vincadifformine (7). Both 1,2-dehydroaspidospermidine (**5**) and aspidospermidine (**6**) were isolated from the bark of the *Aspidosperma quebracho-blanco* tree by Biemann and co-workers in 1961,[19] and vincadifformine (**7**) was obtained from *Vinca difformis* in 1962 by Djerassi, Janot, and co-workers.[20] They belong to the *Aspidosperma* family of alkaloids, which nowadays comprises over 250 members. While aspidospermidine is devoid of significant biological activities, its distinct [6.5.6.6.5] fused pentacyclic structure is found in many bisindole alkaloids such as vincristine and vinblastine that are marketed anticancer drugs.[21] The fascinating molecular architecture of these natural products has inspired significant synthetic efforts. Indeed, as a result of its prominent position among the *Aspidosperma* alkaloids, **6** has been used for decades as a testing ground for new synthetic methodologies. Since Stork's seminal total synthesis of **6** in 1963,[22] many total and formal syntheses have been accomplished by exploring the following strategies (Figure 1):[23] (a) Stork's Fischer indole synthesis of tricyclic aminoketone **18** with phenylhydrazine;[24] (b) Harley-Mason's rearrangement of tetracycle **19**;[25] (c) construction of ABCD tetracycle **20** followed by its elaboration to the ABCDE pentacycle;[26] (d) Diels−Alder reaction (e.g., **21**) for building the key polycyclic intermediate;[27] and others.[28] Consequently, many different synthetic routes have been developed for access to the key intermediates **18**−**21**.

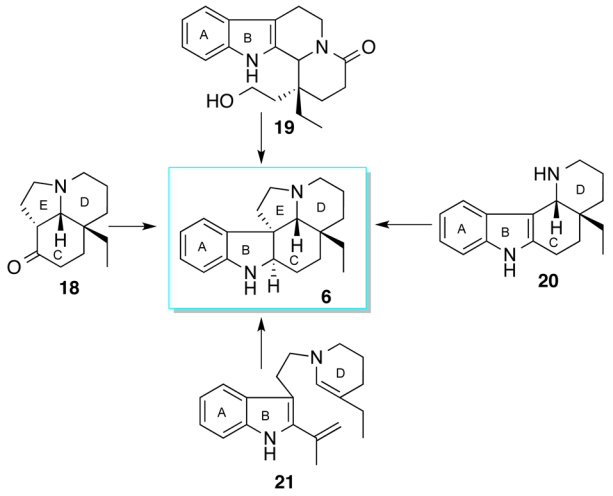
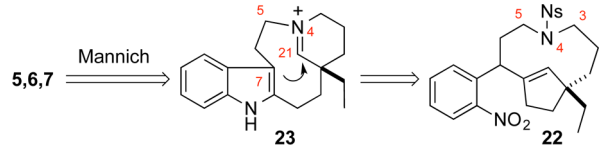


Figure 1. Key intermediates on the way to aspidospermidine (**6**).

In our synthesis of goniomitine, an intramolecular nucleophilic addition of the indolyl nitrogen N1 to C21[29] of the putative iminium intermediate **17** was assumed to be the last step of the *i*ORC sequence.[4] We noticed that an alternative cyclization via nucleophilic addition of C7 (supposed to be more nucleophilic than N1) to C21 was not observed, most probably for steric reasons (cf. Scheme 2). To channel the cyclization via the formation of the C7−C21 bond, we thought to impose a geometric constraint by introducing a C5−N4 bond into the *i*ORC substrate. As shown in Scheme 3, we

Scheme 3. Retrosynthetic Analysis of 1,2-Dehydroaspidospermidine (5)



thought to obtain 1,2-dehydroaspidospermidine (**5**) in one operation by applying the *i*ORC sequence to cyclopentene derivative **22**. Under ideal circumstance, it was expected that the *i*ORC sequence would convert **22** to N^4,C^{21}-dehydroquebrachamine (**23**), which would spontaneously cyclize to **5** via the formation of the C7−C21 bond.[30] Compound **22** can be traced back to **9**, accessible by decarboxylative coupling.

The total synthesis of **5** began with the preparation of macrocycle-bridged cyclopentene **22** (Scheme 4). Pd(0)-catalyzed decarboxylative coupling between potassium 4-[(*tert*-butyldimethylsilyl)oxy]-2-(2′-nitrophenyl)butanoate (**10b**) and vinyl triflate **11b** under our previously optimized conditions[3] followed by workup with TBAF at 0 °C afforded cyclopentene **9b** (57% yield, dr 1:1), in which the TES group was selectively removed without touching the TBS ether. Mitsunobu reaction of **9b** with nosylamine under Walker's conditions[31] followed by addition of TBAF at rt provided nosylamine **24** (71%), which was subsequently converted to macrocycle **22** by a second Mitsunobu reaction (81%). Two diastereomers were separable at this stage, and the structure of one of them was confirmed by single-crystal X-ray structure analysis. Nevertheless, for the sake of convenience, the synthesis was advanced with the mixture of two isomers since the stereogenic center at the benzylic position disappeared at

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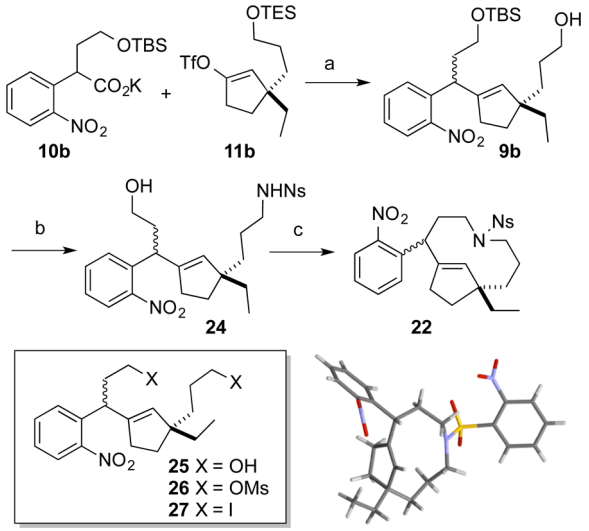
Scheme 4. Synthesis of *i*ORC Substrate 22[a]

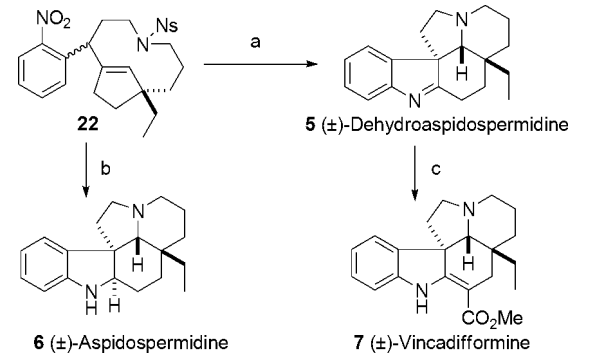


[a]Reagents and conditions: (a) $[Pd(allyl)Cl]_2$ (5.0 mol %), X-Phos (15.0 mol %), diglyme, 100 °C, then TBAF, 0 °C, 57%. (b) PPh_3, DEAD, neopentyl alcohol (40 mol %), toluene, rt, then TBAF, rt, 75%. (c) PPh_3, DEAD, neopentyl alcohol (40 mol %), toluene, rt, 81%.

the end of the synthesis. We also synthesized diol **25**, dimesylate **26**, and diiodide **27**. However, the one-pot double Mitsunobu reaction of **25** or the double S_N2 reaction of **26** or **27** with nosylamine afforded macrocycle **22** in low yields (<25%).

The completion of the syntheses of **5**−**7** by a skeleton-reorganizing *i*ORC process is shown in Scheme 5. Oxidative

Scheme 5. Skeletal Reorganization of Cyclopentene 22: Syntheses of 1,2-Dehydroaspidospermidine (5), Aspidospermidine (6), and Vincadifformine (7)[a]

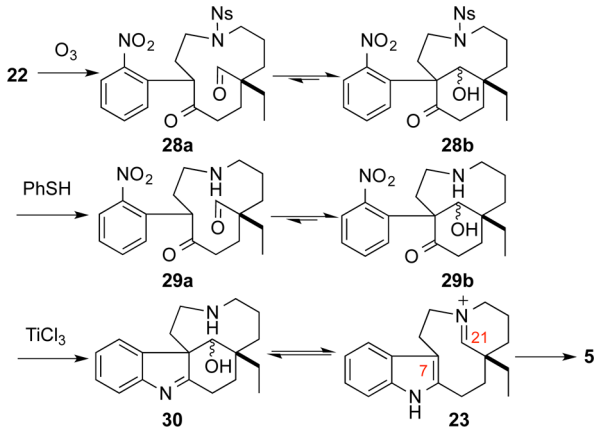


[a]Reagents and conditions: (a) O_3, CH_2Cl_2, Me_2S, then PhSH, Cs_2CO_3, then $TiCl_3$, NH_4OAc, MeOH, 51%. (b) Conditions (a), then aqueous $NaHCO_3$, $NaBH_4$, 50%. (c) *n*BuLi, (1.0 equiv), MeOOCCN (1.6 equiv), 50%.

cleavage of the double bond in **22** with ozone (O_3, CH_2Cl_2, then Me_2S), removal of the *N*-nosyl group under Fukuyama's conditions (PhSH, Cs_2CO_3),[32] and reduction of the nitro group with $TiCl_3$ in an ammonium acetate buffer[33] afforded 1,2-dehydroaspidospermidine (**5**) as the only isolable diastereomer in 51% yield. On the other hand, quenching of the above reaction mixture by the addition of aqueous $NaHCO_3$ solution followed by $NaBH_4$ directly provided aspidospermidine (**6**) in 50% yield. Finally, treatment of **5** with *n*BuLi followed by methyl cyanoformate furnished vincadifformine (**7**) in 50% yield.[27c] The reduction conditions were critical for the above transformation, and the acidity of the reduction medium was of strong importance. Hydrogenation or zinc- or iron-based reduction produced only a trace amount of dehydroaspidospermidine.

A possible reaction pathway accounting for the one-pot conversion of **22** to **5** is depicted in Scheme 6. Oxidative

Scheme 6. Reaction Pathway of the *i*ORC Process



cleavage of cyclopentene **22** followed by removal of the *N*-Ns group afforded 11-membered macrocycle **29a** via **28a**. To understand the reaction pathway, the crude product was analyzed at this stage. We were able to isolate a compound whose structure was tentatively assigned as **29b**, resulting from the intramolecular aldol reaction of **28a** or **29a**. Reduction of the nitro group to aniline was followed by simultaneous cyclization to afford **30**, which might be in equilibrium with N^4,C^{21}-dehydroquebrachamine (**23**) by a sequence of retro-aldol/imine formation. Transannular spirocyclization by nucleophilic addition of C7 onto the iminium carbon C21 from the face opposite to the ethyl group then provided **5** with high diastereoselectivity.[30] We stress that the entire *i*ORC process was performed by sequential addition of reagents in a one-pot fashion without any intermediate workup procedure.

Total Synthesis of Kopsihainanine A (8). Kopsihainanine A (**8**) was isolated by Gao and co-workers in 2011 from the leaves of *Kopsia hainanensis,* a plant used in Chinese medicine.[34] This natural compound has an unusual [6.5.6.6.6] pentacyclic structure, which is a novel structural type among monoterpene indole alkaloids. In addition to the presence of a bridged D/E ring system, the trans-fused C/D ring found in **8** represents a major structural difference relative to other members of the *Aspidosperma* alkaloid family. Three total syntheses and one formal synthesis have been reported using either tetrahydro-4*H*-carbazol-4-one **31** or 2-substituted indole **32** (Figure 2) as a key intermediate.[35]

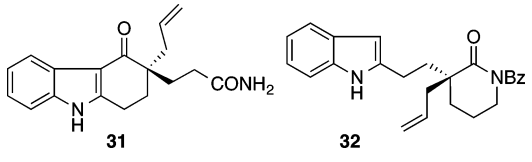


Figure 2. Key intermediates used in previous syntheses of Kopsihainanine A (**8**).

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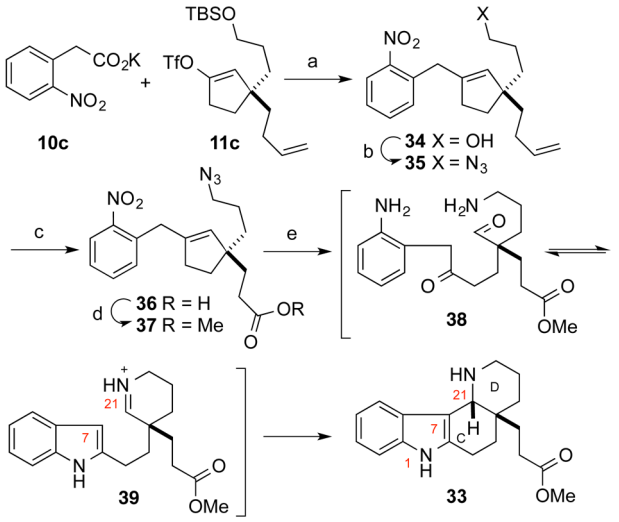
Our initial approach leading to tetracycle **33** with an undesired cis-fused C/D ring is summarized in Scheme 7.

Scheme 7. Synthesis of Tetracycle 33 with a Cis-Fused C/D Ring[a]

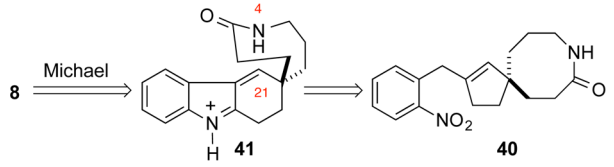


[a]Reagents and conditions: (a) $[Pd(allyl)Cl]_2$ (5.0 mol %), X-Phos (15.0 mol %), diglyme, 100 °C, then TBAF, rt, 88%. (b) Et_3N, MsCl, DMF, rt, then NaN_3, 40 °C, 89%. (c) $KMnO_4$, $NaIO_4$, K_2CO_3, *t*BuOH/H_2O, 45 °C, 72% (83% BRSM). (d) $TMSCHN_2$, MeOH, rt, quantitative. (e) O_3, DCM, −78 °C, then Me_2S, −78 °C to rt, then Zn, HCl, 40%.

Pd(0)-catalyzed decarboxylative coupling between known potassium 2-nitrophenylacetate (**10c**) and vinyl triflate **11c** followed by workup with TBAF at rt afforded alcohol **34** in 88% yield. Treatment of **34** with MsCl and triethylamine (DMF, rt) followed by NaN_3 (40 °C) converted the alcohol to azide **35**. Selective oxidative cleavage of the terminal alkene in the presence of an internal double bond to give *nor*-carboxylic acid **36** was found to be nontrivial. After much experimentation, Lemieux−von Rudloff oxidation was found to be optimal, providing **36** in 83% yield. Compound **36** was converted to methyl ester **37** in quantitative yield.[36] The *i*ORC reaction of **37** (O_3, DCM, then Me_2S, then Zn, HCl) provided compound **33** in 40% yield. Only one diastereomer was isolated, whose structure was determined to be a tetracycle with a cis-fused C/D ring system by comparison with literature data, especially the ^{13}C NMR spectrum.[37] If it is assumed that the reaction went through diamino dicarbonyl intermediate **38** followed by indole **39**, then the observed stereoselectivity is easily understandable by invoking a nucleophilic addition of C7 to the iminium carbon C21 from the face opposite to the neighboring CH_2CH_2COOMe group.

In order to drive the *i*ORC sequence toward the formation of the trans-fused C/D ring found in **8**, we once again thought to impose a geometric constraint on the *i*ORC substrate and targeted spirocycle **40** (Scheme 8). We hypothesized that if the final ring closure were to take place through N4−C21 bond formation in **41** by an intramolecular Michael addition of N4 to the conjugated iminium, we could expect to obtain the desired trans-fused C/D ring system of the natural product. The intermediate **41** could again be derived from spirocycle **40** by an *i*ORC sequence. The latter could be prepared from azido acid **36** via a lactamization reaction. We stress that cyclization

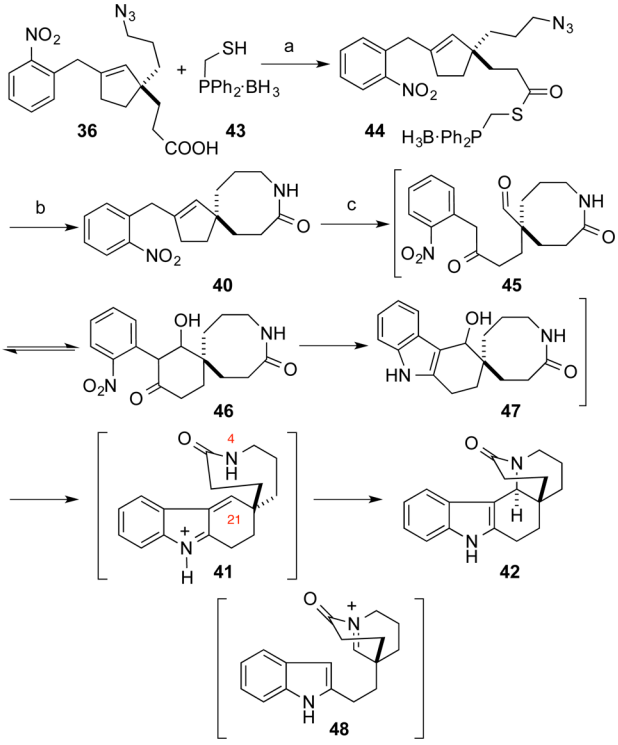
Scheme 8. Retrosynthesis of Kopsihainanine A (8)



of **36** to form the eight-membered lactam **40**, although known to be difficult,[38] is not a redundant step in this case because the so-formed amide bond is an integral part of the natural product.

The synthesis of spirolactam **40** and its subsequent *i*ORC process to form pentacyclic structure **42** of kopsihainanine A is depicted in Scheme 9. While classic lactamization methods

Scheme 9. Synthesis of Pentacycle 42 with a Trans-Fused C/D Ring[a]



[a]Reagents and conditions: (a) HATU, DIPEA, DCM, rt, 91%. (b) DABCO, THF/H_2O, reflux, quantitative. (c) O_3, CH_2Cl_2, −78 °C, then PPh_3 (2.0 equiv), rt, then PtO_2, H_2, then HCl in MeOH, 63%.

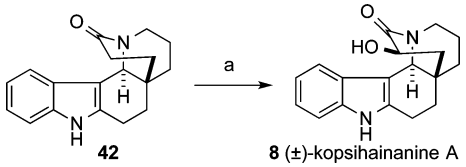
failed, Maarseveen's intramolecular Staudinger ligation method worked efficiently for our purpose.[39] Therefore, coupling of carboxylic acid **36** with borane-protected phosphine **43** (HATU, DIPEA, CH_2Cl_2, rt) furnished thioester **44**. Simply heating to reflux a THF/H_2O solution of **44** in the presence of DABCO afforded spirocycle **40** (91% yield over two steps) by a sequence of decomplexation of the phosphine−borane adduct followed by an intramolecular Staudinger reaction. Conversion of **40** to strained pentacycle **42** by *i*ORC was found to be more difficult than previous *i*ORC processes. After extensive experimentation varying the solvent of ozonolysis and the reductant, the following optimum conditions were found. Oxidative cleavage of the double bond in **40** with ozone (O_3, CH_2Cl_2, then PPh_3) followed by hydrogenation of the nitro group (PtO_2, H_2) and acidic treatment directly afforded

dx.doi.org/10.1021/ja509329x | J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

pentacycle **42** in 63% yield. Raney nickel can also serve as a catalyst to afford **42** in a similar yield. We noted that the use of triphenylphosphine to reduce the ozonide was essential for the success of the overall *i*ORC process. Mechanistically, ozonolysis of **40** would produce keto aldehyde **45**, which might be in equilibrium with spiro intermediate **46**. Reduction of the nitro group would then afford polycyclic indole **47**, which upon acidic workup would furnish pentacyclic product **42** via conjugated iminium intermediate **41**. An alternative pathway going through *N*-acyliminium **48** would afford the cis-fused C/D ring. However, this route might not be competitive because of the high energy associated with the bridgehead double bond.[40]

To conclude the total synthesis of **8**, an α-hydroxylation of the amide was required. While all previous work employed the *N*-benzyl derivative of **42** as a substrate,[35a,b] we decided to perform the α-hydroxylation directly on **42** in order to avoid the protection/deprotection sequence. No desired product was isolated when She's conditions (LDA, Na_2SO_3, O_2, THF) were applied to **42**. After screening of different reaction conditions varying the base, the solvent, the additive, and the oxidant, the optimum conditions were found to consist of performing the reaction in THF/HMPA using lithium dimethylamide (LDMA) as the base and bis(trimethylsilyl)peroxide as the oxidant. Under these conditions, compound **42** was converted stereoselectively to kopsihainanine A (**8**) in 91% yield (Scheme 10). Using LDMA as the base was essential for the success of

Scheme 10. Completion of the Total Synthesis of Kopsihainanine A (8)[a]



42 **8** (±)-kopsihainanine A

[a]Reagents and conditions: (a) LDMA, HMPA, THF, −78 °C to rt, then $(TMSO)_2$, −78 °C to rt, 91%.

the above transformation, as other bulkier bases led essentially to no reaction or degradation depending on the nature of the oxidant. The result is in line with She's observation that the amide enolate is difficult to form because of the steric hindrance around the α-pseudoaxial proton of the amide.

SUMMARY

We have developed concise total syntheses of five *Aspidosperma* alkaloids featuring two key steps: (a) Pd-catalyzed decarboxylative coupling for the synthesis of functionalized cyclopentenes and (b) a one-pot *i*ORC process for skeletal reorganization to convert the cyclopentenes to the pentacyclic structures of the natural products. By incorporating geometric constraints into the *i*ORC substrates, we were able to control both the chemoselectivity (C7 vs N1 cyclization) and the stereoselectivity (trans- vs cis-fused bicyclic ring system) of the cyclization process for the synthesis of the respective targets.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectroscopic data, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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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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