Communication

The Total Synthesis of (+)-Arborisidine

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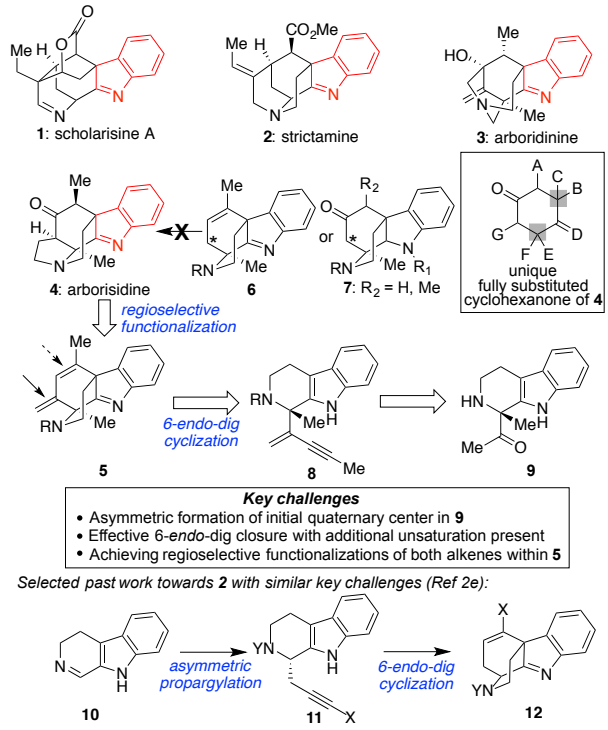
Supporting Information Placeholder

ABSTRACT: The first total synthesis of arborisidine, a unique *Kopsia* indole alkaloid possessing a fully substituted cyclohexanone ring system with two quaternary carbons, has been achieved in 7 steps in racemic format from tryptamine and 9 steps in asymmetric format from D-tryptophan methyl ester. Key elements of the design include a carefully orchestrated decyanation protocol to finalize the asymmetric formation of an *aza*-quaternary center challenging to access in optically active format via direct Pictet–Spengler cyclizations with tryptamine, a metal-promoted 6-*endo*-dig cyclization of an enyne to establish the second core quaternary center, and regiospecific functionalizations of the resultant complex diene to finalize the target structure. The distinct and efficient nature of the developed solution is highlighted by several unsuccessful approaches and unexpected rearrangements.

Over the past several years, efforts to achieve the laboratory synthesis of an array of caged indolenine alkaloids drawn from several plant species have served as a powerful vehicle for driving innovation. Indeed, targets such as scholarisine A (**1**, Scheme 1),[1] strictamine (**2**),[2] and arboridinine (**3**),[3] among others,[4] have proven to be strong tests of available chemical tools, with their constrained frameworks typically necessitating the development of new reactions and synthetic strategies if they are to be fashioned effectively. Arborisidine (**4**)[5] is a recent and valuable addition to this collection, having been isolated and characterized in 2016 in relatively minute quantities (0.2 mg/kg bark) from Malayan *K. Arborea* trees[5] and shown in a patent disclosure to inhibit gastric cancer *in vivo* when used in combination with pimelautide.[6] While **4** shares some general structural features with other caged alkaloids, such as **1**–**3**, its most striking element is its fully substituted cyclohexanone core that includes two quaternary centers, one of which is an *aza*-quaternary carbon that has not yet been observed in related molecules. As highlighted by the only published study towards this target,[7] that core system provides significant synthetic challenges in ways that might not be obvious upon initial inspection. Herein, we describe the first racemic and asymmetric syntheses of this target in 7- and 9-steps, respectively, through a plan featuring several regiospecific and chemoselective events to appropriately fashion its distinctive structural elements.

As shown in Scheme 1, our design for arborisidine (**4**) was predicated on forming its pyrrolidine ring system last. For that event, we anticipated the need to regiospecifically functionalize the exocyclic alkene of diene **5**, either intermolecularly as controlled by stereoelectronic effects or intramolecularly as directed by the adjacent secondary amine. Our desire to use this substrate was based on lessons learned in failed attempts to effect late-stage C–C bond formation from compounds of type **7** (similarly described by Qin)[7] as well as allylic functionalization of **6**, likely due to the considerable conformational strain and steric bulk surrounding the starred methylenes. As a result, we envisioned that the exocyclic olefin of **5** could serve to circumvent these issues by pushing the reactive center away from the steric bulk of the *aza*-quaternary carbon. To fashion that diene, we projected that a 6-*endo*-dig cyclization[2ce] using enyne **8** could rise to the occasion, potentially obtained from aminoketone **9** through nucleophilic addition and alcohol dehydration. As a result, the total synthesis of (+)-**4** would then require an asymmetric synthesis of the lone quaternary center within **9**, an event of high challenge given the paucity of effective enantioselective Pictet–Spengler reactions using ketones.[8,9] However, as we observed in our own efforts with targets such as strictamine (**2**),[2e] the challenges found in forging chiral centers at these positions (as in **10**→**11**) and then effecting cyclization chemistries (as in **11**→**12**) can also afford powerful opportunities for reaction discovery and development.

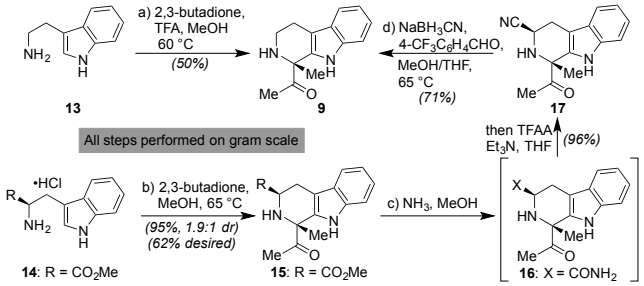
Scheme 1. Structures of Several Alkaloids Containing a Shared Tetracyclic Indolenine Framework and a Generalized Retrosynthetic Plan for Arborisidine (**4**).



Our initial preparation of aminoketone **9** in racemic format proceeded without incident simply by stirring tryptamine (**13**) and 2,3-butadione in acidic MeOH at 60 °C,[10] affording **9** in moderate yield (50%) in the gram-scale quantities needed to probe the remaining elements of the sequence (Scheme 2). By contrast, the means to achieve an asymmetric synthesis of the same compound was non-obvious based on existing Pictet–Spengler precedent, since no substrates of this type in a chiral format have been prepared directly; the closest analogies are a few examples that incorporated α-ketoamides[8] with others utilizing cyclic *N*-acyliminium intermediates.[9] Following initial failures to identify a *de novo* catalytic solution using varied Lewis and phosphoric acid promoters, we wondered if the use of D-tryptophan methyl ester (**14**) could provide an efficient diastereoselective alternative. Strong precedent to that general effect in Pictet–Spengler reactions between both D-/L-tryptophan methyl esters with aldehydes

was known,[11] but not with diketones.[12] Pleasingly, moderate diastereoselectivity could in fact be achieved, favoring the formation of **15** versus its separable diastereomer in a 1.9:1 ratio, leading to an isolated yield of 62% for **15**. Its structure and absolute configuration were confirmed by X-ray analysis of *ent*-**15** formed from initial experiments using L-tryptophan methyl ester.

Scheme 2. Racemic and Enantioselective Syntheses of Aminoketone **9**.[a]



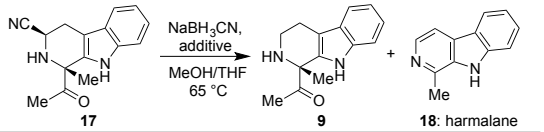
[a] Reagents and conditions: (a) 2,3-butadione (1.1 equiv), TFA (1.0 equiv), MeOH, 60 °C, 20 h, 50%; (b) 2,3-butadione (2.5 equiv), MeOH, 65 °C, 20 h, 95%, 1.9:1 dr, 62% desired diastereomer; (c) NH_3 in MeOH, 23 °C, 15 h; then concentrate; then Et_3N (2.0 equiv), TFAA (1.0 equiv), THF, 23 °C, 1 h; Et_3N (1.0 equiv), TFAA (0.5 equiv), 23 °C, 1.5 h, 96%; (d) 4-trifluoromethylbenzaldehyde (2.6 equiv), $NaBH_3CN$ (2.0 equiv), MeOH/THF, 65 °C, 8 h, 71%.

Despite that success, the added steric bulk and electron-withdrawing effects of the ester and ketone groups α- to the amine made subsequent chemistry quite difficult to achieve. First, efforts to protect the amine were universally non-successful, likely leading to the failures observed when common decarboxylation methods[13] were screened directly with **15**. Thus, we elected to transform that ester into the nitrile of **17** through a one-pot aminolysis/dehydration process,[11b] hoping to effect a seemingly standard decyanation reaction,[14] through reduction of the imine formed via cyanide expulsion, without impacting the ketone. Again, such chemoselectivity proved challenging, but was necessary since if the ketone was reduced, its re-oxidation could not be achieved smoothly in the presence of the free amine. Extensive screening (see SI section for details) ultimately illustrated that $NaBH_3CN$[15] could rise to the occasion; yet, the desired product (**9**) was formed only in low yield as the majority of the material converted instead into the aromatized natural product harmalane (**18**, Table 1, entry 1). That aromatization could not be suppressed even with degassed solution and the addition of BHT as a radical scavenger. Such results led us to believe that the expelled cyanide ion might be involved in the aromatization process in a redox-neutral pathway similar to a retro-benzoin condensation as shown in Scheme 3 via intermediate **20**.

To test this hypothesis, we added benzaldehyde as a cyanide scavenger and, gratifyingly, the yield of aminoketone **9** increased to 50% (Table 1, entry 2). In support of our overall mechanistic hypothesis, the cyanohydrin of benzaldehyde was observed in the ^{1}H NMR spectrum of the crude mixture as was the deuterated cyanohydrin of the expelled methyl ketone when no reductant was present. As shown in the remainder of Table 1, further optimization of the scavenger revealed that more electron-deficient aldehydes were superior, with 4-trifluoromethyl benzaldehyde working best in 69% and 71% yield on test and gram-scale runs, respectively (entries 6 and 7). Finally, although full or partial reduction of the added aldehyde derivatives was observed in all of the experiments listed in entries 2–7, those alcohols had no impact in preventing aromatization as revealed by the control experiment using only added benzyl alcohol (entry 8).

With both racemic and asymmetric routes to **9** secured, we focused next on forming cyclic dienes of type **5** (cf. Scheme 1). As shown in Scheme 4, that goal could be achieved in 3 steps through propyne addition, dehydration of the resultant alcohol as promoted by TFAA (a step that also protected the amine), and a 6-*endo*-dig cyclization[2ce] promoted by a mixture of catalytic amounts of both Au(I) and Ag(I) salts in MeOH at 40 °C. While such *endo* selectivity has been commonly observed in other explorations using similar enynes,[16] most systems studied to date underwent further rearrangements post-cyclization to afford products devoid of an sp^3-hybridized quaternary center. These steps proceeded here in 39% overall yield on gram scale, noting that the yield values shown refer to reactions performed with racemic material; chiral material was advanced as well in commensurate yields, albeit on smaller scales (see SI).

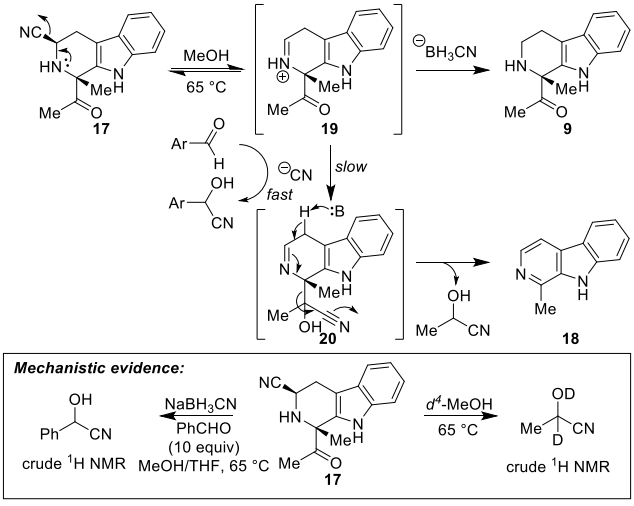
Table 1. Screening of Conditions to Effect Enhanced Preparations of **9** and Minimize the Formation of Aromatic Side Product **18**.



Entry[a]	Additive	Reaction time (h)	Yield **9** (%)[b]
1	none	8	<20[c]
2	C_6H_5CHO	3	50
3	C_6H_5CHO	8	56
4	4-$MeOC_6H_4CHO$	8	42
5	4-ClC_6H_4CHO	8	46
6	4-$CF_3C_6H_4CHO$	8	69
7	4-$CF_3C_6H_4CHO$[d,e]	8	71
8	BnOH	8	13[c]

[a] Conditions: substrate (0.2 to 0.3 mmol), $NaBH_3CN$ (2.0 equiv, 1.0 M in THF), additive (3.0 equiv), MeOH (0.1 M), 65 °C; [b] isolated yield; [c] the major product is **18**; [d] performed on 5 mmol scale; [e] 2.6 equiv of aldehyde was used.

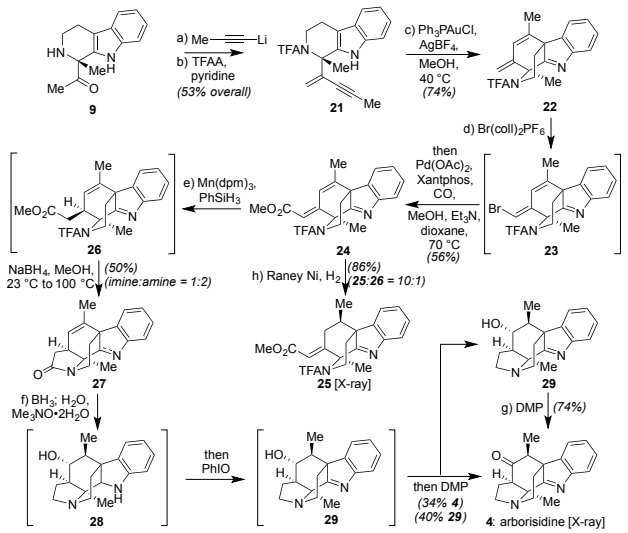
Scheme 3. Proposed Mechanism for the Reductive Decyanation in the Presence of Aromatic Aldehydes.



Differentiation of the diene system was now needed. Initial efforts using polarity-inverse radical additions[17] led either to recovered starting material or decomposition as a result of the generally harsh conditions used for these processes. Fortunately, a regiospecific bromination of the diene motif at its exocyclic terminus could be achieved under mild conditions using bis(2,4,6-trimethylpyridine)bromine(I) hexafluorophosphate;[18] following solvent removal and re-dissolution in 1,4-dioxane, that intermediate could be converted directly into methyl ester **24** in 56% yield through a Pd-catalyzed carbonylation using Xantphos.[19] Of note, the isolated yield of **23** was lower than this one-pot bromination/carbonylation sequence. We attribute this result to the possible formation of an allylic bromide which was unstable to column

purification, but which under the carbonylation conditions could funnel to the desired dienoate through isomerization.

Scheme 4. Completion of the Total Synthesis of Arborisidine (**4**).[a]

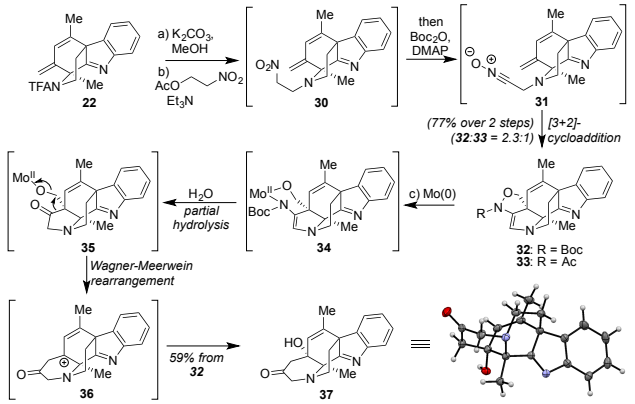


[a] Reagents and conditions: (a) 1-propynyl lithium (4.0 equiv), THF, -78 °C, 2 h; (b) pyridine (3.5 equiv), TFAA (2.2 equiv), CH_2Cl_2, -78 °C to 23 °C, 2 h, 53% for 2 steps; (c) Ph_3PAuCl (0.1 equiv), $AgBF_4$ (0.1 equiv), MeOH, 40 °C, 17 h, 74%; (d) $Br(coll)_2PF_6$ (1.02 equiv), CH_2Cl_2, -78 °C to 23 °C, 1 h; then concentrate; then $Pd(OAc)_2$ (0.02 equiv), Xantphos (0.04 equiv), dioxane/MeOH/Et_3N, CO (balloon), 70 °C, 13 h, 56%; (e) $Mn(dpm)_3$ (0.5 equiv), $PhSiH_3$ (2.0 equiv), *i*-PrOH/$(CH_2Cl)_2$, 23 °C, 10 h; $PhSiH_3$ (1.0 equiv), 23 °C, 7 h; $PhSiH_3$ (1.0 equiv), 23 °C, 4 h; then concentrate; then $NaBH_4$ (10 equiv), MeOH, 23 °C, 1 h; 100 °C, 9 h, 50%, imine/amine = 1:2; (f) BH_3•THF (5.0 equiv), 23 °C, 12 h; then H_2O (2.0 equiv), TMANO•$2H_2O$ (1.1 equiv), THF, 65 °C, 2 h; then concentrate; then PhIO (1.5 equiv), CH_2Cl_2 23 °C, 2.5 h; then $NaHCO_3$ (5.0 equiv), Dess-Martin periodinane (1.5 equiv), 23 °C, 1 h, 34% **4**, 40% **29**; (g) $NaHCO_3$ (5.0 equiv), Dess-Martin periodinane (1.0 equiv), CH_2Cl_2, 23 °C, 30 min, 74%; (h) Raney Ni, THF, H_2 (balloon), 23 °C, 86%, **25**:**26** = 10:1. $Br(coll)_2PF_6$ = bis(2,4,6-trimethylpyridine)bromine(I) hexafluorophosphate; TMANO•$2H_2O$ = trimethylamine *N*-oxide dehydrate.

From here, we next sought to achieve a regioselective 1,4-reduction to generate **26**; such an operation was viewed as feasible based on three-dimensional models showing that the β-position within this framework should be more accessible than the δ-position, with the hydride source adding from the less-hindered *Si*-face. However, conventional dienoate hydrogenation[20abc] and conjugate reduction[20d] methods either provided no conversion, no selectivity, or, in the case of Raney Nickel,[20e] predominately 1,6-reduction to generate **25** (structure confirmed by X-ray crystallographic analysis) with a 10:1 preference over **26**. Inspired by the pioneering work of Magnus[21ab] and Shenvi[21c] in manganese-catalyzed hydrogen atom transfer processes (HAT), a reaction that was previously of high use to us in the synthesis of another complex alkaloid,[21d] we were pleased to find that such conditions could deliver the desired 1,4-reduction product exclusively. Extensive optimization (see SI for more details) showed that the use of $Mn(dpm)_3$ in a 50 mol % loading in combination with $PhSiH_3$ gave the best conversion, using trace air as the activator[21b] of the catalyst. When conducted on larger scales (>50 mg), the portion-wise addition of $PhSiH_3$ in excessive amounts was necessary to achieve full conversion, but at the price of the extra silane causing challenges in purification. As a result, the crude mixture of **26** was treated directly, following initial solvent evaporation, with methanolic $NaBH_4$. This operation excised the trifluoroacetamide protecting group, effected lactam formation, and afforded partial reduction of the indolenine system. The resultant mixture of imine and amine products (separable for purposes of characterization but also readily purified as a mixture) was then exposed to a carefully executed sequence in hope of affording arborisidine (**4**) directly. Those operations included initial treatment with excess BH_3 in THF to effect alkene hydroboration and full imine and lactam reduction. After quenching any remaining BH_3 with H_2O, the resultant alkylborane was oxidized into a secondary alcohol using Me$_3$NO•$2H_2O$,[22] with PhIO[23] then added to oxidize the dihydroindole domain, and Dess–Martin periodinane (DMP)[24] added last to oxidize the secondary alcohol. Upon quenching, this one-pot operation afforded arborisidine (**4**) in 34% yield along with partially oxidized **29** in 40% yield. As such, a 7-step racemic synthesis (and 9-step asymmetric synthesis) of the target was achieved, with material supplies of the natural product enhanced by the separate oxidation of **29** using DMP. Pleasingly, all spectral and optical rotation data of **4** matched that of the natural sample as reported by Kam and co-workers[5] with its structure further confirmed by X-ray analysis. To date, close to 50 mg of **4** has been accumulated (~40 mg racemic, ~5 mg asymmetric) from all runs of the sequence.

As one example of the uniqueness of the developed solution in terms of advancing forward from diene **22** through intermolecular chemo- and regioselective tranforms, significant efforts were also made to reach the target through intramolecular cyclizations as tethered by the adjoining N-atom of the *aza*-quaternary center. Scheme 5 documents one such attempt, where an intramolecular nitrile-oxide [3+2]-cycloaddition[25] with partial *N*-acylation could smoothly deliver a mixture of **32** and **33**. Unfortunately, subsequent N–O bond cleavage of **32** using freshly prepared $Mo(CO)_3(MeCN)_3$,[26] while successful, also initiated an unexpected Wagner–Meerwein-type rearrangement affording **37** as the sole identifiable product (confirmed by X-ray). Attempts to ring-contract this material were not successful.

Scheme 5. Attempted Intramolecular [3+2]-Cycloaddition and an Unexpected Rearrangement.[a]



[a] Reagents and conditions: (a) K_2CO_3 (4.0 equiv), MeOH, 60 °C, 4 h; (b) Et_3N (5.0 equiv), $AcOCH_2CH_2NO_2$ (1.1 equiv), THF, 23 °C, 2 h; then 4-DMAP (0.2 equiv), Boc_2O (2.0 equiv), 23 °C, 20 h; 4-DMAP (0.2 equiv), Boc_2O (2.6 equiv), 23 °C, 7 h, 77% for two steps, **32**:**33** = 2.3:1; (c) $Mo(CO)_3(MeCN)_3$ (4.0 equiv), $MeCN/CH_2Cl_2/H_2O$, 23 °C, 1 h, 59% from **32**.

In conclusion, this work highlights a number of unique operations leading to the first total synthesis of the caged alkaloid arborisidine (**4**). Most critical among those steps were 1) a chemoselective reductive decyanation strategy which affords access to chiral 1,1-disubstituted 3,4-dihydro-β-carbolines that are currently inaccessible via direct asymmetric Pictet–Spengler reactions with diketones, 2) an effective 6-*endo*-dig cyclization of an enyne leading to a cyclic diene, 3) regiospecific differentiation and functionalization of that resultant diene system, and 4) a carefully orchestrated oxidation state adjustment achieved in one pot. Overall, the brevity of the developed solution should inform strategies to access other alkaloids with hopefully similar expediency.

ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, copies of all spectral data, cif files, and full characterization. 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.

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REFERENCES

(1) (a) Adams, G. L.; Carroll, P. J.; Smith, III, A. B. Total Synthesis of (+)-Scholarisine A. *J. Am. Chem. Soc.* **2012**, *134*, 4037–4040; (b) Smith, M. W.; Snyder, S. A. A Concise Total Synthesis of (+)-Scholarisine A Empowered by a Unique C–H Arylation. *J. Am. Chem. Soc.* **2013**, *135*, 12964–12967; (c) Adams, G. L.; Carroll, P. J.; Smith, III, A. B. Access to the Akuammiline Family of Alkaloids: Total Synthesis of (+)-Scholarisine A. *J. Am. Chem. Soc.* **2013**, *135*, 519–528.

(2) (a) Moreno, J.; Picazo, E.; Morrill, L. A.; Smith, J. M.; Garg, N. K. Enantioselective Total Syntheses of Akuammiline Alkaloids (+)-Strictamine, (–)-2(*S*)-Cathafoline, and (–)-Aspidophylline A. *J. Am. Chem. Soc.* **2016**, *138*, 1162–1165; (b) Ren, W.; Wang, Q.; Zhu, J. Total Synthesis of (±)-Strictamine. *Angew. Chem. Int. Ed.* **2016**, *55*, 3500–3503; (c) Nishiyama, D.; Ohara, A.; Chiba, H.; Kumagai, H.; Oishi, S.; Fujii, N.; Ohno, H. Formal Total Synthesis of (±)-Strictamine Based on a Gold-Catalyzed Cyclization. *Org. Lett.* **2016**, *18*, 1670–1673; (d) Eckermann, R.; Breunig, M.; Gaich, T. Formal total synthesis of (±)-strictamine – the [2,3]-Stevens rearrangement for construction of octahydro-2*H*-2,8-methanoquinolizines. *Chem. Commun.* **2016**, *52*, 11363–11365; (e) Smith, M. W.; Zhou, Z.; Gao, A. X.; Shimbayashi, T.; Snyder, S. A. A 7-Step Formal Asymmetric Total Synthesis of Strictamine via an Asymmetric Propargylation and Metal-Mediated Cyclization. *Org. Lett.* **2017**, *19*, 1004–1007; (f) Eckermann, R.; Breunig, M.; Gaich, T. Formal Total Synthesis of (±)-Strictamine by [2,3]-Sigmatropic Stevens Rearrangements. *Chem. Eur. J.* **2017**, *23*, 3938–3949; (g) Xie, X.; Wei, B.; Li, G.; Zu, L. Unified Total Syntheses of Structurally Diverse Akuammiline Alkaloids. *Org. Lett.* **2017**, *19*, 5430–5433; (h) Xiao, T.; Chen, Z.; Deng, L.; Zhang, D.; Liu, X.-Y.; Song, H.; Qin, Y. Formal total synthesis of the akuammiline alkaloid (+)-strictamine. *Chem. Commun.* **2017**, *53*, 12665–12667; (i) Sato, K.; Takanashi, N.; Kogure, N.; Kitajima, M.; Takayama, H. Formal Total Synthesis of (±)-Strictamine. *Heterocycles* **2018**, *97*, 365–382; (j) Chen, Z.-T.; Xiao, T.; Tang, P.; Zhang, D.; Qin, Y. Total synthesis of akuammiline alkaloid (+)-strictamine. *Tetrahedron* **2018**, *74*, 1129–1134; (k) Picazo, E.; Morrill, L. A.; Susick, R. B.; Moreno, J.; Smith, J. M.; Garg, N. K. Enantioselective Total Syntheses of Methanoquinolizidine Containing Akuammiline Alkaloids and Related Studies. *J. Am. Chem. Soc.* **2018**, *140*, 6483–6492; (l) Li, W.; Chen, Z.; Yu, D.; Peng, X.; Wen, G.; Wang, S.; Xue, F.; Liu, X.-Y.; Qin, Y. Asymmetric Total Syntheses of the Akuammiline Alkaloids (–)-Strictamine and (–)-Rhazinoline. *Angew. Chem. Int. Ed.* **2019**, *58*, 6059–6063; for a recent review, see (m) Wang, C.; Zhang, S.; Wang, Y.; Huang, S.-H.; Hong, R. Total synthesis of strictamine: a tutorial for novel and efficient synthesis. *Org. Chem. Front.* **2018**, *5*, 447–452.

(3) (a) Gan, P.; Pitzen, J.; Qu, P. Snyder, S. A. Total Synthesis of the Caged Indole Alkaloid Arboridinine Enabled by *aza*-Prins and Metal-Mediated Cyclizations. *J. Am. Chem. Soc.* **2018**, *140*, 919–925; (b) Zhang, Z.; Xie, S.; Cheng, B.; Zhai, H.; Li, Y. Enantioselective Total Synthesis of (+)-Arboridinine. *J. Am. Chem. Soc.* **2019**, *141*, DOI: 10.1021/jacs.9b02362.

(4) For recent total syntheses of other complex akuammiline indolenine alkaloids, see: Xiang Zhang, X.; Kakde, B. N.; Guo, R.; Yadav, S.; Gu, Y.; Li, A. Total Syntheses of Echitamine, Akuammiline, Rhazicine, and Pseudoakuammigine. *Angew. Chem. Int. Ed.* **2019**, *58*, 6053–6058.

(5) Wong, S.-P.; Chong, K.-W.; Lim, K.-H.; Lim, S.- H.; Low, Y.-Y.; Kam, T.-S. Arborisidine and Arbornamine, Two Monoterpenoid Indole Alkaloids with New Polycyclic Carbon–Nitrogen Skeletons Derived from a Common Pericine Precursor. *Org. Lett.* **2016**, *18*, 1618–1621

(6) Zhuang, H.; Wei, S. Medicine composition for inhibiting stomach cancer. 2016, Patent: CN106540237A.

(7) Chen, Z.; Xiao, T.; Song, H.; Qin, Y. Asymmetric Synthesis of the Tetracyclic Skeleton of Natural Product Arborisidine. *Chin. J. Org. Chem.* **2018**, *38*, 2427–2434.

(8) (a) Bou-Hamdan, F. R.; Leighton, J. L. Highly Enantioselective Pictet–Spengler Reactions with α-Ketoamide-Derived Ketimines: Access to an Unusual Class of Quaternary α-Amino Amides. *Angew. Chem. Int. Ed.* **2009**, *48*, 2403–2406; (b) Duce, S.; Pesciaioli, F.; Gramigna, L.; Bernardi, L.; Mazzanti, A.; Ricci, A.; Bartoli, G.; Bencivenni, G. An Easy Entry to Optically Active Spiroindolinones: Chiral Brønsted Acid-Catalysed Pictet–Spengler Reactions of Isatins. *Adv. Synth. Catal.* **2011**, *353*, 860–864; (c) Dai, W.; Lu, H.; Li, X.; Shi, F.; Tu, S. J. Diastereo- and Enantioselective Construction of a Bispirooxindole Scaffold Containing a Tetrahydro-β-carboline Moiety through an Organocatalytic Asymmetric Cascade Reaction. *Chem. Eur. J.* **2014**, *20*, 11382–11389; (d) Piemontesi, C.; Wang, Q.; and Zhu, J. Enantioselective Synthesis of (+)-Peganumine A. *J. Am. Chem. Soc.* **2016**, *138*, 11148–11151.

(9) (a) Raheem, I. T.; Thiara, P. S.; Peterson, E. A.; Jacobsen, E. N. Enantioselective Pictet-Spengler-Type Cyclizations of Hydroxylactams: H-Bond Donor Catalysis by Anion Binding. *J. Am. Chem. Soc.* **2007**, *129*, 13404–13405; (b) Muratore, M. E.; Holloway, C. A.; Pilling, A. W.; Storer, R. I.; Trevitt, G.; Dixon, D. J. Enantioselective Brønsted Acid-Catalyzed *N*-Acyliminium Cyclization Cascades. *J. Am. Chem. Soc.* **2009**, *131*, 10796–10797; (c) Holloway, C. A.; Muratore, M. E.; Storer, R. I.; Dixon, D. J. Direct Enantioselective Brønsted Acid Catalyzed N-Acyliminium Cyclization Cascades of Tryptamines and Ketoacids. *Org. Lett.* **2010**, *12*, 4720–4723; (d) Cai, Q.; Liang, X.-W.; Wang, S.-G.; Zhang, J.-W.; Zhang, X.; You, S.-L. Ring-Closing Metathesis/Isomerization/Pictet-Spengler Cascade via Ruthenium/ Chiral Phosphoric Acid Sequential Catalysis. *Org. Lett.* **2012**, *14*, 5022–5025; (e) Gregory, A. W.; Jakubec, P.; Turner, P.; Dixon, D. J. Gold and BINOL-Phosphoric Acid Catalyzed Enantioselective Hydroamination/N-Sulfonyliminium Cyclization Cascade. *Org. Lett.* **2013**, *15*, 4330–4333.

(10) Kuehne, M. E. Process for the preparation of (+,–) vincadifformine and other related pentacyclic derivatives. 1978, Patent: EP0011059A1.

(11) (a) Nakagawa, M.; Fukushima, H.; Kawate, T.; Hongu, M.; Une, T. Kodato, S.; Taniguchi, M.; Hino, T. Synthetic Approaches to Fumitremorgins. III. Synthesis of Optically Active Pentacyclic Ring Systems, and Their Oxidation at Ring C. *Chem. Pharm. Bull.* **1989**, *37*, 23–32; (b) Pellegrini, C.; Weber, M.; Borschberg, H.-J. 15. Total Synthesis of (+)-Elacomine and (–)-Isoelacomine, Two Hitherto Unnamed Oxindole Alkaloids from *Elueagnus cornrnutata*. *Helv. Chim. Acta,* **1996**, *79*, 151–168.

(12) There are two examples of Pictet–Spengler reactions between tryptophan and ketones, but the presence of the carboxylic acid rendered the products water soluble, necessitating recrystallization/lyophilization for purification; we found these methods impractical. (a) Bobbitt, J. M.; Willis, J. P. Electrochemistry of Natural Products. 7. Oxidative Decarboxylation of Some Tetrahydro-β-carbolinecarboxylic Acids. *J. Org. Chem.* **1980**, *45*, 1978–1984; (b) Kuo, F.-M.; Tseng, M.-C.; Yen, Y.-H.; Chu, Y.-H. Microwave Accelerated Pictet–Spengler Reactions of Tryptophan with Ketones Directed Toward The Preparation of 1,1-Disubstituted Indole Alkaloids. *Tetrahedron* **2004**, *60*, 12075–12084. For examples of Pictet–Spengler reactions between tryptophan methyl ester and ketones, see: (c) Horiguchi, Y.; Nakamura, M.; Saitoh, T.; Sano, T. A Synthesis of Chiral 1,1,3-Trisubstituted 1,2,3,4-Tetrahydro-β-carbolines by the Pictet–Spengler Reaction of Tryptophan and Ketones: Conversion of (1*R*,3*S*)-Diastereomers into Their (1*S*,3*S*)-Counterparts by Scission of the C(1)–N(2) Bond. *Chem. Pharm. Bull.* **2003**, *51*, 1368–1373; (d) Kulkarni, A. S.; Shingare, R. D.; Dandela, R.; Reddy, D. R. Total Synthesis of an Anticancer Natural Product (±)-Peharmaline A and Its Analogues. *Eur. J. Org. Chem.* **2018**, 6453–6456.

(13) (a) Barton, D. H. R.; Samadi, M. The Invention of Radical Reactions. Part XXV. A Convenient Method for the Synthesis of the Acyl Derivatives of *N*-Hydroxypyridine-2-Thione. *Tetrahedron* **1992**, *48,* 7083–7090; (b) Yang, J.; Zhang, J.; Qi, Li.; Hu, C.; Chen, Y. Visible-Light-Induced Chemoselective Reductive Decarboxylative Alkynylation under Biomolecule-Compatible Conditions. *Chem. Commun*. **2015**, *51*, 5275–5278; (c) Qin, T.; Malins, L. R.; Edwards, J. T.; Merchant, R. R.; Novak, A. J. E.; Zhong, J. Z.; Mills, R. B.; Yan, M.; Yuan, C.; Eastgate, M. D.; Baran, P. S. Nickel-Catalyzed Barton Decarboxylation and Giese Reactions: A Practical Take on Classic Transforms. *Angew. Chem. Int. Ed*. **2017**, *56*, 260–265; (d) Griffin, J. D.; Zeller, M. A.; Nicewicz, D. A. Hydrodecarboxylation of Carboxylic and Malonic Acid Derivatives via Organic Photoredox Catalysis: Substrate Scope and Mechanistic Insight. *J. Am. Chem. Soc*. **2015**, *137*, 11340–11348; (e) Cassani, C.; Bergonzini, G.; Wallentin, C.-J. Photocatalytic Decarboxylative Reduction of Carboxylic Acids and Its Application in Asymmetric Synthesis. *Org. Lett*. **2014**, *16*, 4228–4231.

(14) For a recent review, see: Mattalia, J.-M. R. The Reductive Decyanation Reaction: An Overview and Recent Developments. *Beilstein J. Org. Chem*. **2017**, *13*, 267–284.

(15) Baldwin, J. E.; Spring, D. R.; Whitehead, R. C. A Novel Diels–Alder Approach to Hydroisoquinolines. *Tetrahedron Lett*. **1998**, *39*, 5417–5420.

(16) (a) Lu, Y.; Du, X.; Jia, X.; Liu, Y. Gold-Catalyzed Intermolecular Reactions of (Z)-Enynols with Indoles for the Construction of Dihydrocyclohepta[b]indole Skeletons through a Cascade Friedel–Crafts/Hydroarylation Sequence. *Adv. Synth. Catal*. **2009**, *351*, 1517 – 1522; (b) Chen, Y.; Liu, Y. Gold-Catalyzed Approach to Multisubstituted Fulvenes via Cycloisomerization of Furan/Ynes. *J. Org. Chem*. **2011**, *76*, 5274–5282; (c) Sun, N.; Xie, X.; Liu, Y. Gold-Catalyzed Cascade Reactions of Furan-ynes with External Nucleophiles Consisting of a 1,2-Rearrangement: Straightforward Synthesis of Multi-Substituted Benzo[*b*]furans. *Chem. Eur. J*. **2014**, *20*, 7514–7519.

(17) (a) Taniguchi, T.; Sugiura, Y.; Zaimoku, H.; Ishibashi, H. Iron-Catalyzed Oxidative Addition of Alkoxycarbonyl Radicals to Alkenes with Carbazates and Air. *Angew. Chem. Int. Ed*. **2010**, *49*, 10154–10157; (b) Kamijo, S.; Yokosaka, S.; Inoue, M. Attachment of Carbonyl Functionalities onto Olefins via Copper-Promoted Radical Reaction of Dichloromethylcyanides. *Tetrahedron* **2012**, *68*, 5290–5296.

(18) Homsi, F.; Robin, S.; Rousseau, G. Preparation of Bis(2,4,6-Trimethylpyridine)Iodine(I) Hexafluorophosphate and Bis(2,4,6-Trimethylpyridine) Bromine(I) Hexafluorophosphate. *Org. Synth*. **2000**, *77*, 206–211.

(19) Martinelli, J. R.; Watson, D. A.; Freckmann, D. M. M.; Barder, T. E.; Buchwald, S. L. Palladium-Catalyzed Carbonylation Reactions of Aryl Bromides at Atmospheric Pressure: A General System Based on Xantphos. *J. Org. Chem*. **2008**, *73*, 7102–7107.

(20) (a) Ma, J.; Yin, W.; Zhou, H.; Liao, X.; Cook, J. M. General Approach to the Total Synthesis of 9-Methoxy-Substituted Indole Alkaloids: Synthesis of Mitragynine, as well as 9-Methoxygeissoschizol and 9-Methoxy-N_b-methylgeissoschizol. *J. Org. Chem*. **2009**, *74*, 264–273; (b) Renata, H.; Zhou, Q.; Dünstl, G.; Felding, J.; Merchant, R. R.; Yeh, C.-H.; Baran, P. S. Development of a Concise Synthesis of Ouabagenin and Hydroxylated Corticosteroid Analogues. *J. Am. Chem. Soc*. **2015**, *137*, 1330–1340; (c) Hugelshofer, C. L.; Magauer, T. Total Synthesis of the Leucosceptroid Family of Natural Products. *J. Am. Chem. Soc*. **2015**, *137*, 3807–3810; (d) Baker, B. A.; Boskovic, Z. V.; Lipshutz, B. H. (BDP)CuH: A "Hot" Stryker's Reagent for Use in Achiral Conjugate Reductions. *Org. Lett*. **2008**, *10*, 289–292; (e) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R.; Meneses, R. Raney Nickel: An Efficient Reagent to Achieve the Chemoselective Hydrogenation of α,β-Unsaturated Carbonyl Compounds. *Synlett* **1999**, *10*, 1663–1666.

(21) (a) Magnus, P.; Waring, M. J.; Scott, D. A. Conjugate reduction of α,β-unsaturated ketones using an Mn^{III} catalyst, phenylsilane and isopropyl alcohol. *Tetrahedron Lett*. **2000**, *41*, 9731–9733; (b) Magnus, P.; Payne, A. H.; Waring, M. J.; Scott, D. A.; Lynch, V. Conversion of α,β-unsaturated ketones into α-hydroxy ketones using an Mn^{III} catalyst, phenylsilane and dioxygen: acceleration of conjugate hydride reduction by dioxygen. *Tetrahedron Lett*. **2000**, *41*, 9725–9730; (c) Iwasaki, K.; Wan, K. K.; Oppedisano, A.; Crossley, S. W. M.; Shenvi, R. A. Simple, Chemoselective Hydrogenation with Thermodynamic Stereocontrol. *J. Am. Chem. Soc*. **2014**, *136*, 1300–1303; (d) Gao, A. X.; Hamada, T.; Snyder, S. A. The Enantioselective Total Synthesis of Exochomine. *Angew. Chem. Int. Ed*. **2016**, *55*, 10301–10306.

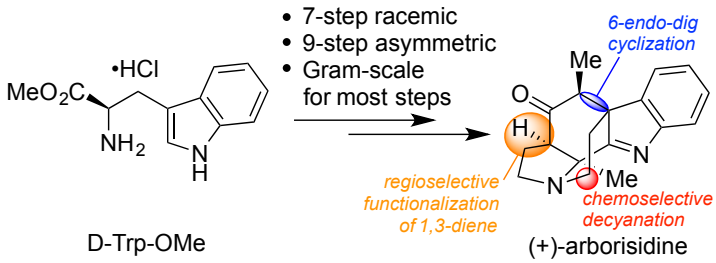
(22) (a) Kabalka, G. W.; Hedgecock Jr., H. C. A Mild and Convenient Oxidation Procedure for the Conversion of Organoboranes to the Corresponding Alcohols. *J. Org. Chem*. **1975**, *40*, 1776–1779; (b) Kabalka, G. W.; Slayden, S. W. Oxidation of Organobosanes with Triethylamine N-oxide Dihydrate. *J. Organomet. Chem*. **1977**, *125*, 273–280. (c) Donohoe, T. J.; O'Riordan, T. J. C.; Peifer, M.; Jones, C. R.; Miles, T. J. Asymmetric Synthesis of the Fully Elaborated Pyrrolidinone Core of Oxazolomycin A. *Org. Lett*. **2012**, *14*, 5460–5463.

(23) Muller, P.; Gilabert, D. M. Oxidation of amines to imines with hypervalent iodine. *Tetrahedron* **1988**, *44*, 7171–7175.

(24) Dess, D. B.; Martin, J. C. Readily accessible 12-I-5 oxidant for the conversion of primary and secondary alcohols to aldehydes and ketones. *J. Org. Chem*. **1983**, *48*, 4155–4156.

(25) Prasad, S. S.; Senthilkumar, S.; Srivastava, A.; Baskaran, S. Iminosugar *C*-Nitromethyl Glycosides and Divergent Synthesis of Bicyclic Iminosugars. *Org. Lett*. **2017**, *19*, 4403–4406; (b) Prasad, S. S.; Baskaran, S. Iminosugar *C*-Nitromethyl Glycoside: Stereoselective Synthesis of Isoxazoline and Isoxazole-Fused Bicyclic Iminosugars. *J. Org. Chem*. **2018**, *83*, 1558–1564.

(26) (a) Tate, D. P.; Knipple, W. R.; Augl, J. M. Nitrile Derivatives of Chromium Group Metal Carbonyls. *Inorg. Chem*. **1962**, *1*, 433–434; (b) Kobayashi, T.; Nitta, M. Hexacarbonylmolybdenum-induced Reaction of Isoxazoles. Cycloaddition of Isoxazoles with Acetylenic Esters and Related Reactions. *Bull. Chem. Soc. Jpn*. **1985**, *58*, 152–157; (c) Guarna, A.; Guidi, A.; Goti, A.; Brandi, A.; De Sarlo, F. Cleavage of Isoxazolines with Tricarbonyltris(acetonitrile)molybdenum and Silica Gel. Synthesis of 1-(2-Oxoalkyl)cyclopropanols from Isoxazoline-5-spirocyclopropanes. *Synthesis* **1989**, 175–178.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