Convergent Total Synthesis of (–)-Cyclopamine

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ABSTRACT: A concise and enantioselective total synthesis of the *Veratrum* alkaloid cyclopamine is disclosed. This highly convergent synthesis with a 15-step longest linear sequence (LLS) was enabled by a *de novo* synthesis of the *trans*-6,5 hetero-bicycle *via* a strain-inducing halocyclization process, a key Tsuji-Trost cyclization to construct the fully substituted, spirocyclic THF motif with exquisite diastereocontrol, and a late-stage ring-closing metathesis (RCM) reaction to forge the central tetrasubstituted olefin.

Cyclopamine (**1**), first isolated from *Veratrum californicum* (California corn lily)[1], is a notable member of the *Veratrum* alkaloid family (Figure 1A).[2] It is known *ex post facto* for inducing the cyclopia birth defect in sheep, where the affected new-born lambs only had one eye and were reminiscent of the cyclops from Greek mythology.[3] Studies from Beachy et al. revealed that cyclopamine is a potent inhibitor of the highly conserved hedgehog signaling pathway, which is critical for the correct differentiation and symmetry development of embryos.[4] Despite its known decomposition pathway leading to veratramine (**3**) and other byproducts under acidic conditions[5], cyclopamine has been recognized as a promising anti-cancer agent and numerous medicinal analogs have been reported to date, most notably saridegib (**4**) which was prepared semi-synthetically.[6]

The intricate structures of *Veratrum* alkaloids have piqued the interest of synthetic chemists for years.[7] With respect to cyclopamine, the rare C-*nor*-D-*homo* steroid skeleton is further complicated by the fully substituted, spirocyclic THF motif, the unique *trans*-6,5 EF ring system, and the central tetrasubstituted olefin, all of which posed unique challenges to its synthesis. A pioneering synthesis of the closely related jervine (**2**) by Masamune et al. involves an 18-step sequence starting from the advanced intermediate **6**, which in turn must be prepared in 25 steps from Hagemann's ester or obtained from degradation of hecogenin.[7a] More recently in 2009, Giannis et al. disclosed an elegant semi-synthesis of cyclopamine in 20 steps from dehydroepiandrosterone (**5**), featuring a biomimetic 1,2-skeletal rearrangement to construct the C-*nor*-D-*homo* steroid scaffold.[7h] Multiple progress-towards studies of jervine or cyclopamine have also been reported to date.[8] This Communication discloses a convergent and enantioselective total synthesis of **1** with a 15-step LLS.

The final retrosynthetic depiction shown in Figure 1B benefitted from the learnings of multiple generations of unsuccessful routes, most of which were based on the convergent union of ABC and EF fragments followed by D-ring formation post-coupling (see SI for details). Learnings from those studies led to the current approach wherein a fully formed ABC tricycle (Fragment A, **7**) was coupled to an EF bicycle

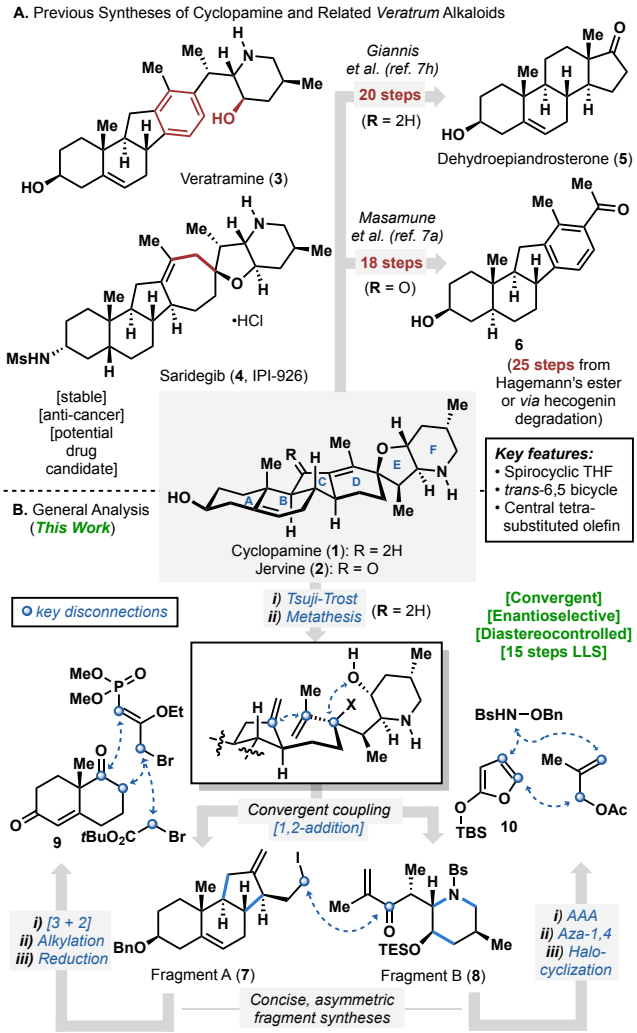
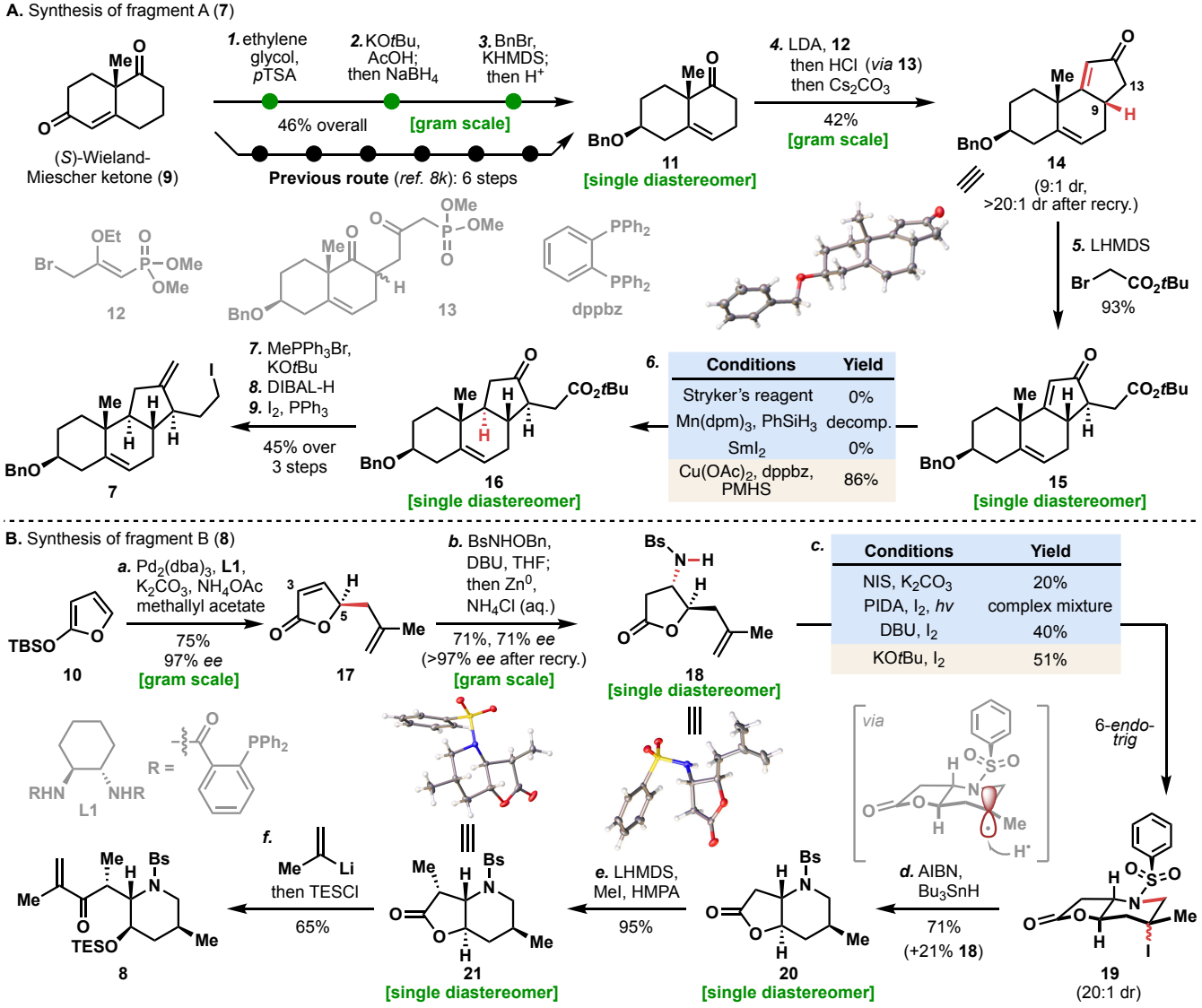


Figure 1. Cyclopamine (**1**): (A) related family members, medicinal analogs, and previous syntheses; (B) retrosynthetic analysis in this work.

Scheme 1. Synthesis of fragments A (**7**) and B (**8**).[a]

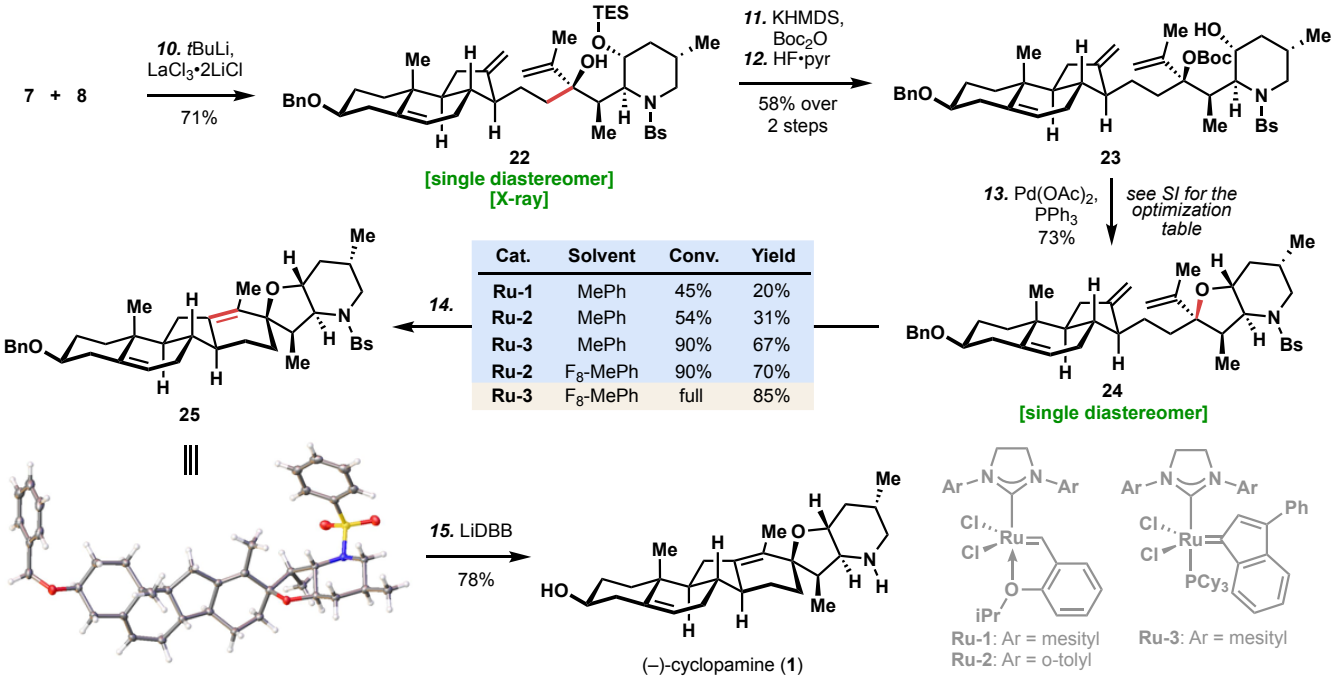


[a] For detailed reagents and conditions, see Supporting Information.

progenitor (Fragment B, **8**) *via* a diastereoselective 1,2-addition. The late-stage formation of the D/E ring systems hinged on a Tsuji-Trost cyclization to forge the THF ring and an RCM reaction to build the central tetrasubstituted olefin. **7** and **8** could in turn be prepared from readily available building blocks such as (*S*)-Wieland Miescher ketone (**9**) and 2-siloxyfuran **10**.

The synthesis of **7** (Scheme 1A) commenced from the decalin **11**, previously prepared in 6 steps from (*S*)-Wieland-Miescher ketone (**9**).[8k] A convenient, scalable 3-step protocol was thus developed involving enone isomerization/reduction of acetal protected **9** (see SI for details). A cyclopentenone annulation sequence was subsequently carried out using the known phosphonate reagent **12**[9]: the lithium enolate of **11** was first alkylated with **12** to afford intermediate **13** as a 1:1 mixture of C9 epimers (after hydrolysis of the enol ether), which upon treatment with Cs_2CO_3 underwent an intramolecular Horner-Wadsworth-Emmons reaction to forge the cyclopentenone motif with concomitant equilibration to a 9:1 mixture of C9 epimers favoring the desired diastereomer, as confirmed by X-ray crystallographic analysis. Further enrichment of **14** to >20:1 dr was achieved after a single round of recrystallization from hexanes/DCM (*ca.* 10:1). With gram quantities of **14** at hand, a second enolate alkylation at C13 with *tert*-butyl bromoacetate proceeded smoothly to yield **15** as a single diastereomer. The conjugate reduction of enone **15** required judicious choice of reagents (see SI for the full optimization table). Whereas Stryker's reagent and SmI_2 gave no reaction and Shenvi's HAT reduction conditions[10] resulted in decomposition, a reactive CuH species reported by Lipshutz *et al.*[11] proved to be the optimal choice, furnishing the desired 1,4-reduction product **16** in 86% yield as a single diastereomer without any undesired 1,2-reduction. Ketone **16** was ultimately transformed to the 1,2-addition precursor **7** by Wittig olefination, DIBAL-H reduction of the *t*Bu ester, and finally an Appel reaction to convert the resulting primary alcohol to iodide.

Scheme 2. Total synthesis of (–)-cyclopamine (1).[a]



[a] For detailed reagents and conditions, see Supporting Information.

Multiple strategies (see SI) to access fragment B (**8**) were evaluated *via* a structure such as lactone **20** (Scheme 1B). Similar molecules have been prepared in the past through labor-intensive chiral pool strategies. For instance, a derivative of **20** bearing a Cbz instead of a benzenesulfonyl (Bs) group was previously accessed in either 9 steps[8c] or 6 steps[8h] from (*S*)-citronellal, with 2 additional steps required to exchange the PG as the sulfonamide protecting group has proven to be essential for late-stage manipulations (see SI for discussion). A concise 4-step route to **20** was thus developed through an unusual sequence relying on the C5-selective asymmetric allylic alkylation (AAA) of siloxyfuran **10** as reported by Arseniyadis *et al.*[12] This key precedent was improved for the synthesis of γ-butenolide **17** through the addition of NH_4OAc (as per suggested by the Arseniyadis group in our correspondence) which further boosted reaction efficiency and regioselectivity (favoring C5 allylation over C3), delivering **17** in 75% isolated yield and 97% *ee* (see SI for details). Subsequent aza-Michael addition to **17** required substantial screening (see SI) that eventually led to the identification of BsNHOBn (*N*-benzenesulfonyl-*O*-benzylhydroxylamine) as the optimal nucleophile. X-ray analysis confirmed that addition occurred exclusively *trans* to the existing γ substituent on the butenolide. In its fully optimized form, this reaction involved directly treating the aza-Michael adduct with Zn^0/NH_4Cl in the same reaction vessel to effect N-O bond cleavage and furnish the sulfonamide **18** as a single diastereomer in 71% isolated yield. Racemization of **18** (71% *ee*) was observed but could be rectified by a single round of recrystallization from DCM/Et_2O (1:1), which restored its enantiopurity (>97% *ee*). With gram quantities of **18** at hand, the key halocyclization step to construct the strained *trans*-6,5 EF bicycle was investigated. Due to the extreme strain that would be incurred through a 5-*exo-trig* cyclization to deliver a *trans*-5,5 ring system, it was rationalized that an unusual 6-*endo-trig* cyclization would be preferred. After the initial hit with NIS/K_2CO_3 verified this hypothesis, further screening was performed (see SI for details) that eventually led to the most reproducible and scalable protocol with KO*t*Bu/I_2. In its fully optimized form, the halocyclization step furnished the tertiary iodide **19** in 51% yield as a 20:1 mixture of diastereomers, which were subjected to a tin hydride-mediated dehalogenation reaction to afford the desired lactone **20** in 71% yield as a single diastereomer. This stereochemical outcome could be rationalized as a combination of thermodynamic preference (methyl group prefers to be equatorial) and steric bulk of the benzenesulfonyl group (which disfavors hydride approach from top face of the tertiary radical). It is worth noting that the ring-opening side product **18** was consistently observed on larger scale (>100 mg) and could be isolated in 21% yield. Attempts to suppress this process by running the reaction at ambient temperature instead of 100 °C (see SI) surprisingly exacerbated ring-opening (**20**:**18** = 1:1, vs. 3:1 with AIBN at 100 °C). Besides this piece of evidence, we also observed that 1) the halocyclization reaction exhibited certain degrees of reversibility over prolonged reaction times (see SI), and 2) addition of TEMPO to the halocyclization reaction inhibited product formation. These clues led us to speculate that the halocylization might proceed through a one-electron pathway involving formation and homolysis of an N-I species (see SI). Methylation of **20** by enolate alkylation proceeded smoothly to deliver the key lactone **21** as a single diastereomer, the structure of which was confirmed by X-ray analysis. Finally, addition of isopropenyllithium to lactone **21**, followed by simultaneous ring-chain tautomerization of the resulting hemiketal and TES protection of the secondary alcohol, furnished enone **8** in 65% yield over this one-pot sequence.

With both fragments (**7** and **8**) in hand, the endgame sequence (Scheme 2) commenced with union of the two fragments by 1,2-addition, wherein the primary iodide **7** first underwent lithium halogen exchange with *t*BuLi, and then the resulting alkyllithium species added into enone **8**. Addition of $LaCl_3$•2LiCl proved to be crucial (see SI for additive screening) for the exclusive 1,2-regioselectivity observed in this reaction[13], yielding tertiary alcohol **22** as a single diastereomer (confirmed by X-ray) possibly due to Felkin-Ahn selectivity. This success set the stage for the final D/E ring double cyclization sequence, which entailed formation of the E ring through an alkoxide Tsuji-Trost cyclization followed by formation of the D ring by ring-closing metathesis (RCM). The challenging Tsuji-Trost cyclization turned out to be an immense undertaking that required considerable optimization (see SI). To our delight, Boc carbonate **23** (prepared from **22** in two steps) emerged as the singularly successful substrate, delivering the desired THF-containing RCM precursor **24** in 73% yield with perfect net stereoretention from tertiary alcohol **22**. This diastereochemical outcome was in line with previous observations in similar THF-forming Tsuji-Trost cyclizations.[14] The RCM reaction to form the tetrasubstituted olefin, which was the final hurdle in this synthesis, was initially met with expected difficulties (see SI for details): conventional metathesis catalysts such as Hoveyda-Grubbs 2nd generation catalyst (**Ru-1**) gave low conversions even at elevated temperatures, and the less sterically encumbering *o*-tolyl variant **Ru-2** only led to slightly improved results. Fortunately, the indenylidene catalyst **Ru-3** was reported to be an extremely effective metathesis catalyst for sterically demanding substrates.[15] Indeed, a significant improvement in yield was observed with **Ru-3**, which, when combined with perfluorotoluene[15b] as solvent, led to the optimal condition that afforded bis-protected cyclopamine **25** in 85% yield, the structure of which was confirmed by X-ray analysis. The prior approach of Giannis necessitated two distinct reductive deprotection conditions to excise Bn and sulfonamide groups.[7h] Instead, removal of both groups could be accomplished with freshly prepared LiDBB[16], yielding (–)-cyclopamine in 78% yield. It is worth noting that we observed significant concentration dependence when acquiring the NMR spectra of cyclopamine in CD_2Cl_2, a solvent that was used in multiple previous reports (see SI for discussion).

To conclude, a convergent total synthesis of (–)-cyclopamine (**1**) was achieved with a 15-step LLS (62% ideality) from (*S*)-Wieland-Miescher ketone. Unlike the semi-synthetic routes which predate this disclosure, the strategy outlined herein should be amenable to exploring deep-seated structural modifications for further SAR studies of this promising class of natural products. Key areas for improvement for which there are methodological gaps include a more direct conversion of **18** to **20** (see SI for discussion) and a more concise fragment coupling that can minimize PG-manipulations. That said, notable features of this synthesis include rapid stereocontrolled access to similarly sized coupling fragments, namely the streamlined ABC-ring synthesis through annulation/CuH reduction and an unusually concise furan-based access to the key EF ring system via AAA/aza-Michael/halocyclization. Furthermore, the exquisite stereocontrol exhibited in the fragment coupling/strained THF ring formation prior to the high-yielding RCM cyclization represents a bold yet effective means of accessing **1**.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Detailed experimental procedures and analytical data (PDF)

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GRAPHICAL ABSTRACT