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Progress toward a Convergent, Asymmetric Synthesis of Jervine

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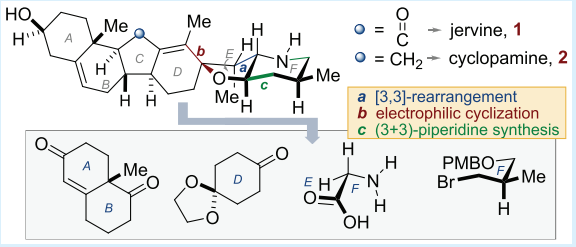
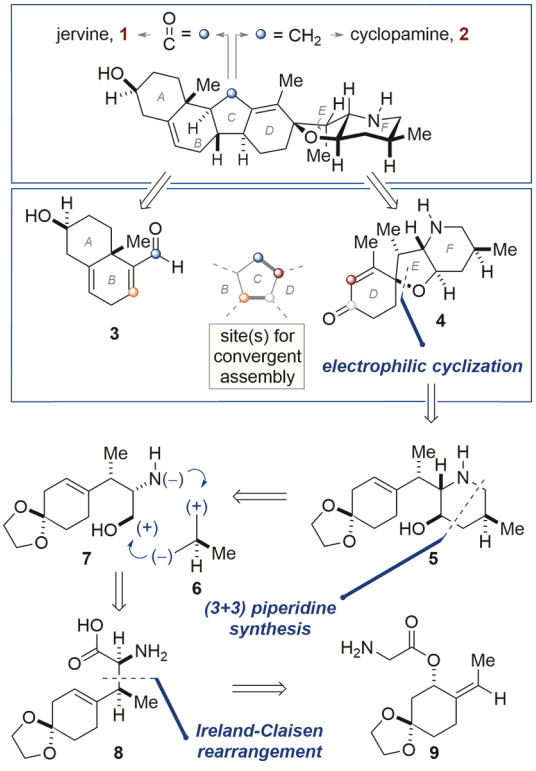
ABSTRACT: Progress toward a convergent approach for the enantioselective synthesis of the *Veratrum* alkaloid jervine is presented. The two requisite fragments were stereoselectively and efficiently fashioned from economical and readily available reagents. Key reactions include (a) a highly diastereoselective Ireland−Claisen rearrangement to establish the necessary *cis*-relationship between the amine and methyl group on the tetrahydrofuran E-ring; (b) a diastereoselective selenoetherification reaction that enabled the assembly of the D/E oxaspiro[4.5]decene in the needed configuration; and (c) an enzymatic desymmetrization of an abundant achiral diol en route to a key four-carbon building block as a practical alternative to a protected Roche ester reduction.



The *Veratrum* alkaloids comprise more than 20 unique natural product scaffolds, many of which exhibit biological activity in cardiovascular, neuromuscular, and respiratory actions. These poisonous plants have garnered attention as therapeutics as early as the Middle Ages, finding applications such as fever medications, sedatives, cardiotonics, and emetics.[1] In 1837, it was discovered that the plant *Veratrum album* contained an alkaloidal base, which was given the name jervine (**1**, Scheme 1).[2] The molecule was not isolated as a single compound until 1879, when it was extracted from the same source by Luff and Alder Wright.[3] The first report of the deoxygenated relative of jervine, cyclopamine (**2**, Scheme 1), did not occur until 1957, found as a result of an investigation by the United States Department of Agriculture into sheep in Idaho displaying alobar holoprosencephaly.[4] In addition to exhibiting teratogenic effects, this class of compounds shows promising biological activity. In 1998, it was shown that cyclopamine interacts with the protein Smoothened, resulting in inhibition of the hedgehog signaling pathway.[5] Overexpression of this pathway in adults has been implicated in the onset of certain types of cancers such as basal cell carcinoma, medulloblastoma, rhabdomyosarcoma, and prostate, pancreatic, and breast cancers. Though the seminal discovery of a small molecule regulating the hedgehog signaling pathway was only 20 years ago, hedgehog-pathway inhibitors have already shown promise as anticancer therapeutics.[6]

Along with their biological profiles, the complex structural features of these molecules have attracted significant attention from the synthetic community. The C-*nor*-D-*homo* steroid skeleton found in both alkaloids contains an unusual 6−6−5−6 ABCD core (Scheme 1), compared to the more commonly observed 6−6−6−5 ABCD steroidal structure. Additionally, grafted onto the D ring via spirocyclic linkage exists a densely functionalized tetrahydrofuran fused to a substituted piper-

Scheme 1. Synthetic Plan for *Veratrum* Alkaloid Natural Products



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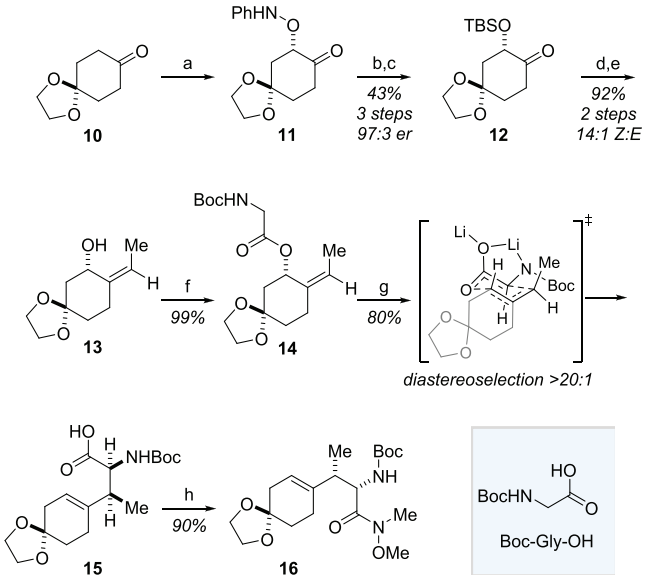
idine, a heterocyclic array underrepresented in the literature. Further complicating synthetic considerations is the tendency of the tetrahydrofuran ring to fragment when exposed to acidic conditions.[7] Early syntheses of jervine by Masamune (1967)[8] and Warnock (1975)[9] were landmark achievements in complex molecule synthesis and showcased the power of utilizing a convergent strategy toward the *Veratrum* alkaloids. In 2009, Giannis and co-workers took a semisynthetic approach, elegantly elaborating the steroid dehydroepiandrosterone to cyclopamine in only 20 steps.[10] Despite these excellent reports,[11] we believe that we could access new chemical space with a novel, de novo synthesis of jervine, with the intent of preparing analogues of jervine to analyze the impact of these modifications in structure−activity studies.

With the goal of a convergent synthesis in mind, jervine was first separated into a Wieland−Miescher ketone[12] derived steroidal fragment (**3**) and alkaloid fragment (**4**, Scheme 1). Initial focus was placed on constructing alkaloid tricycle **4**. Deconstruction of the spiro linkage through a projected electrophilic cyclization onto a trisubstituted olefin led to the secondary alcohol **5**. Disconnection of the piperidine ring through deployment of an appropriate synthetic equivalent for the linchpin synthon **6**[13] led to the γ,δ-unsaturated acid **8**, which constitutes a retron for a glycine-based Ireland−Claisen rearrangement.

Our first task in testing this hypothesis was the synthesis of alkylidene cyclohexane **14** (Scheme 2). The known nitrosobenzene-based α-functionalization[14] using ketone **10** delivered α-oxygenated product **11** in excellent enantioselectivity (97:3 enantiomeric ratio (er)). After an aqueous workup, N−O bond cleavage could be achieved using copper(II) sulfate pentahydrate in methanol, an economical alternative to the known N−O bond cleavage using Pd/C and hydrogen gas.[15] Because of the poor stability of the resulting free alcohol, the unpurified product was immediately protected to afford the stable silyl-protected ketol **12** in 43% yield over three steps. The Wittig olefination of ketol **12** proceeded in good selectivity when the alcohol was protected with bulky protecting groups.[16] Subsequent silyl ether deprotection and esterification furnished (*Z*)-allylic glycinate ester **14** in excellent yield. Initial attempts to perform the Claisen rearrangement of **14** were performed by transmetalation of the lithium enolate using strongly chelating metals, but these conditions provided poor yields and diastereoselectivities.[17] In contrast to literature precedent,[17] standard Ireland−Claisen conditions[18] employed on Boc-protected glycinate **14** smoothly delivered rearranged amino acid product **15** in 80% yield and greater than 20:1 diastereomeric ratio (dr). Finally, amidation provided the Weinreb amide **16** in excellent yield (90%).

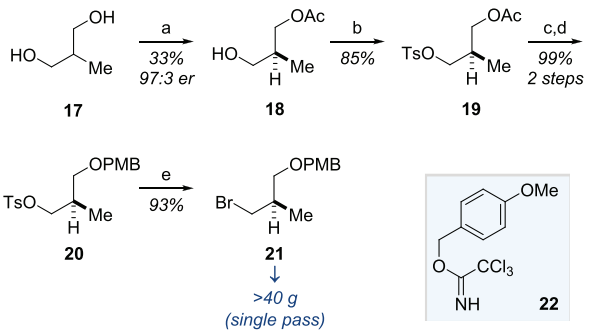
Our next objective was to develop a scalable synthesis of an appropriate synthetic equivalent to the dipolar synthon **6** necessary for piperidine ring closure. We targeted the alkyl bromide **21** (Scheme 3). While this compound has been

Scheme 2. Synthesis of Weinreb Amide 16[a,b]



[a]Reagents and conditions: (a) D-proline (10 mol %), nitrosobenzene (1 equiv), DMF, 0 °C; (b) $CuSO_4{\cdot}5H_2O$ (30 mol %), MeOH, 0 °C; (c) TBSCl (2.5 equiv), imidazole (5 equiv), DMF, 0 °C to rt; (d) ethyltriphenylphosphonium bromide (2.3 equiv), ^{n}BuLi (2.2 equiv), THF, 0 °C to rt; (e) TBAF·H_2O (3 equiv), THF, 0 °C to rt; (f) Boc-Gly-OH (2 equiv), CDI (2 equiv), DBU (2 equiv), THF, 0 °C to rt; (g) LDA (3 equiv), then TMSCl (3 equiv), THF, −78 °C to reflux; (h) CDI (1.1 equiv), *N,O*-dimethylhydroxylamine hydrochloride (1.6 equiv), CH_2Cl_2, 0 °C to rt. [b]Reported diastereoselectivities and *Z*/*E* ratios represent kinetic selectivities of the reaction. Compounds were isolated at slightly less enriched ratios, as some synthetic steps resulted in small degradation of ratios and/or mixtures of isomers that were inseparable. See the Supporting Information for details.

Scheme 3. Synthesis of Linchpin 21 through Enzymatic Resolution[a]



[a]Reagents and conditions: (a) *Pseudomonas fluorescens* lipase (5 g of catalyst per mole of diol), vinyl acetate (4 equiv), $CHCl_3$, 30 °C; (b) TsCl (2 equiv), NEt_3 (3 equiv), DMAP (15 mol %), CH_2Cl_2, 0 °C; (c) K_2CO_3 (2 equiv), MeOH, 0 °C; (d) PPTS (10 mol %), **22** (2 equiv), CH_2Cl_2, 0 °C to rt; (e) LiBr (3 equiv), THF, 0 °C to reflux.

described in the literature,[19] we believed that the conventional method of starting from the Roche ester was prohibitively costly. We instead began with the enantioselective enzymatic acylation of 2-methyl-1,3,-propanediol (**17**), in which a moderately stereoselective desymmetrization is followed by a highly selective kinetic resolution of the intermediate monoacetate.[20] Despite the modest yield of enantioenriched acetate **18**, the low price of the reagents was attractive, and the loading of the catalyst was decreased to 5 g of catalyst per mole of diol. The desired direct conversion of alcohol **18** to its corresponding alkyl bromide via the Appel reaction[21] was not feasible due to a degradation of enantioselectivity in the reaction, presumably arising from formation of an achiral intermediate via an intramolecular substitution reaction. Instead, alcohol **18** was first converted to its derived tosylate

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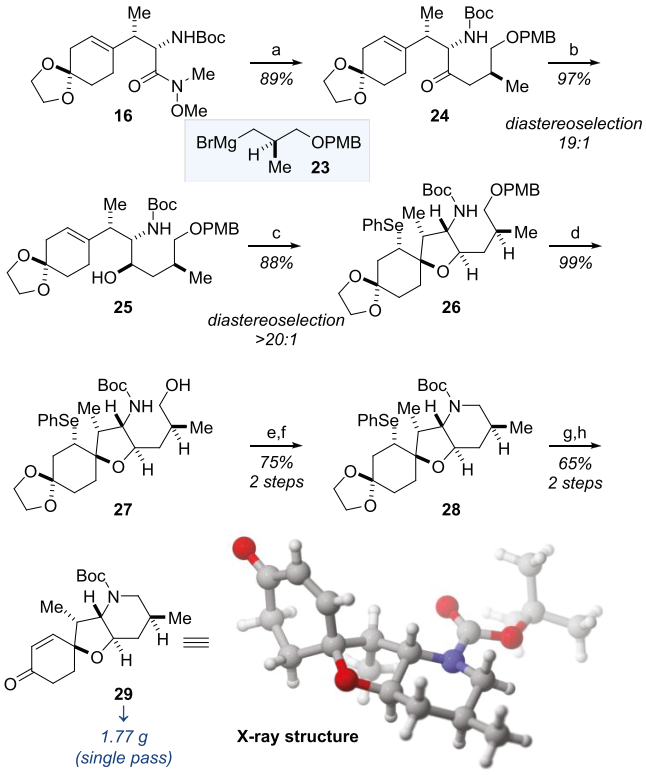
in 85% yield, which was followed by a protecting group exchange from an acetate ester to a *para*-methoxybenzyl (PMB) ether. This sequence resulted in a nearly quantitative yield of PMB ether **20**. Heating tosylate **20** at reflux in the presence of LiBr afforded enantioenriched alkyl bromide **21** in 93% yield. This route proved scalable, and more than 40 g of ether **21** was obtained in a single pass.

After obtaining sufficient quantities of alkyl bromide **21**, we were positioned to test the key organometallic addition. The Grignard reagent **23** derived from the bromide **21** added smoothly to the magnesium salt of **16**, proceeding in 89% yield (Scheme 4). A chelation-controlled reduction using diisobutylaluminium hydride (DIBAL-H) gave amino alcohol stereotetrad **25** (97%, diastereoselection 19:1). The selenoetherification of **25** proceeded in good yield and stereoselectivity,[22] and the stereochemical identity was verified via X-ray crystallographic analysis of a downstream intermediate.[23] Closure of the F-ring was accomplished by deprotection of PMB ether **26** and subsequent conversion of the free primary alcohol into a mesylate, which under basic conditions formed piperidine **28** in 75% yield over two steps. At this stage, completion of the alkaloid fragment **29** hinged upon successful manipulation of the cyclohexane ring to the requisite cyclohexenone. Hydrolysis of the dioxolane protecting group needed to be performed under carefully prescribed conditions (Fe(III), 0 °C)[24] to avoid cleavage of the acid-sensitive spirocyclic linkage. Finally, selenoxide elimination[25] formed eastern fragment **29** (65% over two steps, 1.77 g obtained in one pass). An X-ray crystallography experiment was performed on this compound, which confirmed the molecule's connectivity and stereochemistry.[23]

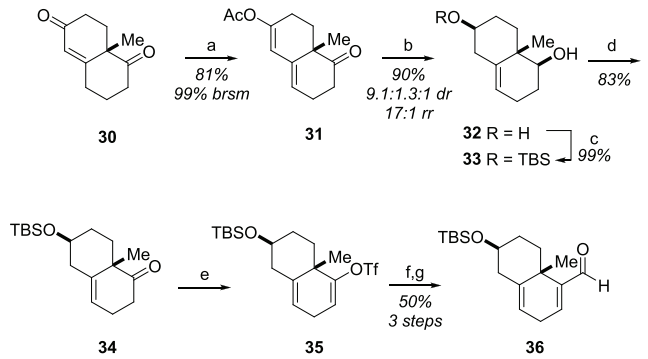
Scheme 4. Completion of Alkaloid Fragment[a,b] 29 and X-ray Crystallography Experiment[23]



[a]Reagents and conditions: (a) EtMgBr (0.95 equiv), then **23** (2.5 equiv), Et_2O, 0 °C to rt; (b) DIBAL-H (3 equiv), PhMe, −78 °C; (c) PhSeBr (1.4 equiv), pyridine (1.7 equiv), CH_2Cl_2, 0 °C; (d) DDQ (1.15 equiv), CH_2Cl_2/H_2O, 0 °C; (e) MsCl (2 equiv), NEt_3 (3.5 equiv), CH_2Cl_2, 0 °C; (f) KO^{t}Bu (1.6 equiv), THF, 0 °C; (g) $FeCl_3 \cdot 6H_2O$ (3.5 equiv), CH_2Cl_2/acetone, 0 °C; (h) H_2O_2 (2 equiv), pyridine (3 equiv), CH_2Cl_2, 0 °C. Enone **29** was isolated as an 18:1 mixture of diastereomers. [b]Reported diastereoselectivities represent kinetic selectivities of the reaction. Some compounds were isolated as slightly less-enriched ratios, as some synthetic steps resulted in small degradation of the ratio of diastereomers and/or the diastereomers were inseparable. See the Supporting Information for details.

The Wieland−Miescher ketone[12] represents a logical point of embarkation for the western fragment but presented two major challenges: alkene migration and carbon−carbon bond formation at the neopentyl position. We opted to first effect olefin migration by formation of vinyl acetate **31** followed by sodium borohydride reduction,[26] which formed diol **32** in 9.1:1.3:1 dr and as a 17:1 mix of alkene isomers, which was separated at a later stage (Scheme 5). Next, diol **32** was selectively protected as a monosilyl ether in 99% yield. Swern oxidation[27] and subsequent vinyl triflate synthesis[28] provided **35**, setting the stage for the key carbon−carbon bond-forming reaction. After vinyl triflate **35** and the corresponding vinyl iodide proved recalcitrant to carbonylation, we identified the Stille coupling of vinyl triflate **35** and Bu_3SnCH_2OH[29] as a method to complete the final carbon framework for the western fragment. Oxidation of the resulting alcohol using the Dess−Martin periodinane[30] (50% yield over three steps) furnished enal **36** in seven steps from the Wieland−Miescher ketone. The enone functionality in tricycle **29** presents the opportunity for introduction of a methyl cuprate followed by aldol-based fragment coupling with aldehyde **36**; however, initial attempts at enolate addition were hampered by the poor electrophilicity of enal **36**. Future work will explore various C-ring cyclopentannulation strategies that leverage the extant B- and D-ring functionality.

Scheme 5. Synthesis of Western Fragment[a]



[a]Reagents and conditions: (a) Ac_2O (6 equiv), $TsOH \cdot H_2O$ (3 mol %), PhMe, reflux; (b) $NaBH_4$ (6 equiv), EtOH, 0 °C to rt; (c) TBSCl (1.5 equiv), imidazole (2 equiv), CH_2Cl_2, rt; (d) oxalyl chloride (2.5 equiv), DMSO (5 equiv), NEt_3 (8 equiv), CH_2Cl_2, −78 °C to rt; (e) KHMDS (2 equiv), $PhNTf_2$ (2.5 equiv), THF, −78 °C to rt; (f) Bu_3SnCH_2OH (2.2 equiv), $Pd(PPh_3)_4$ (5 mol %), LiCl (3 equiv), THF, reflux; (g) Dess−Martin periodinane (1.2 equiv), sodium bicarbonate (3 equiv), CH_2Cl_2, 0 °C.

The *Veratrum* alkaloids continue to pose a formidable challenge to synthetic chemists due to their size, array of stereogenic centers, and *sui generis* substructures. In this work,

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the foundation for a scalable, convergent approach was realized, assembling the carbon skeleton and seven stereocenters of jervine using simple reagents and practical, catalytic sources of chirality (D-proline, L-proline, and *Pseudomonas fluorescens* lipase). This route provides every carbon needed for the target structure except for the D-ring methyl group, and it is highlighted by the use of robust Ireland–Claisen and selenoetherification reactions in order to stereoselectively assemble a fully substituted spiro-tetrahydrofuran ring.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00972.

Experimental procedures, analytical data for new compounds, and NMR spectra (PDF)

Accession Codes

CCDC 1986262 (**29**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44 1223 336033.

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Notes

The authors declare no competing financial interest.

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