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Divergent syntheses of complex *Veratrum* alkaloids

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The *Veratrum* alkaloids are a class of highly intricate natural products renowned for their complex structural and stereochemical characteristics, which underlie a diverse array of pharmacological activities ranging from antihypertensive properties to antimicrobial effects. These properties have generated substantial interest among both synthetic chemists and biologists. While numerous advancements have been made in the synthesis of jervanine and veratramine subtypes over the past 50 years, the total synthesis of highly oxidized cevanine subtypes has remained relatively scarce. Building on the efficiency of our previously developed strategy for constructing the hexacyclic carbon skeleton of the *Veratrum* alkaloid family via a stereoselective intramolecular Diels-Alder reaction and radical cyclization, here we show the development of a unified synthetic approach to access highly oxidized *Veratrum* alkaloids. This includes the total synthesis of (−)-zygadenine, (−)-germine, (−)-protoverine and the alkamine of veramadine A, by capitalizing on a meticulously designed sequence of redox manipulations and a late-stage neighboring-group participation strategy.

The *Veratrum* alkaloids constitute a family of steroidal alkaloids characterized by a unique *C*-nor-*D*-homo steroid skeleton (Fig. 1). These alkaloids are widely distributed across various species of *Veratrum* and *Zigadenus*, comprising three subtypes (jervanine, veratramine, cevanine) and encompassing over 200 compounds[1–3]. Notably, several members of this alkaloid family are recognized for their distinctive biological activities or toxic effects. For instance, cyclopamine and jervine exhibit pronounced teratogenicity by blocking the Hedgehog signaling pathway[4–6]; zygadenine, found in death camas species, induces poisoning in livestock[7,8]; germine and protoverine demonstrate antihypertensive properties[9,10], and veratridine binds to voltage-gated sodium channels, acting as either an agonist or antagonist in a context- and subtype-dependent manner[11–13]. The intricate structures and significant biological activities of these compounds have sparked considerable interest within both the synthetic and biological research communities.

Over the past 50 years, continuous synthetic breakthroughs have significantly advanced the synthesis of the jervanine and veratramine subtypes. In 1967, Masamune's group and Johnson's group independently achieved the synthesis of jervine and veratramine, respectively[14–16]. Kutney's group reported the total synthesis of verarine in 1976[17], employing a strategy involving the hydrogenation of a pyridine unit to construct the F ring; they subsequently applied the same strategy in the synthesis of verticine[18,19]. In 2009, Giannis' group introduced a semisynthetic route to cyclopamine[20], while in 2023, both Baran's group[21] and Gao's group[22] separately disclosed the total synthesis of (−)-cyclopamine. Most recently, in 2024, Qin, Liu and coworkers reported divergent and gram-scale syntheses of (−)-veratramine and (−)-cyclopamine from dehydro-*epi*-androsterone in an efficient manner[23]. Shifting focus to the cevanine subtype, Rawal's group achieved the synthesis of (+)-heilonine in 2021[24], and more recently in 2024. Dai's group also reported its synthesis[25].

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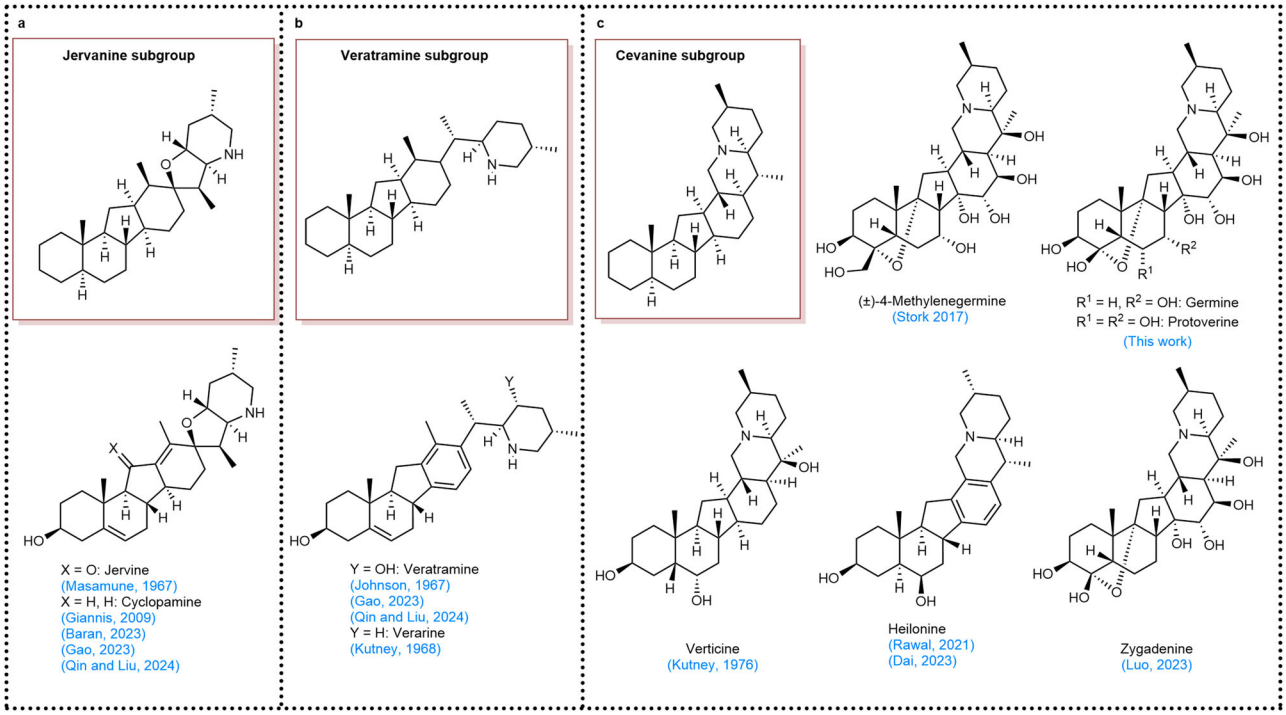

Fig. 1 | Reported syntheses of *Veratrum* alkaloids. a Framework of the jervanine subgroup. **b** Framework of the veratramine subgroup. **c** Framework of the cevanine subgroup.

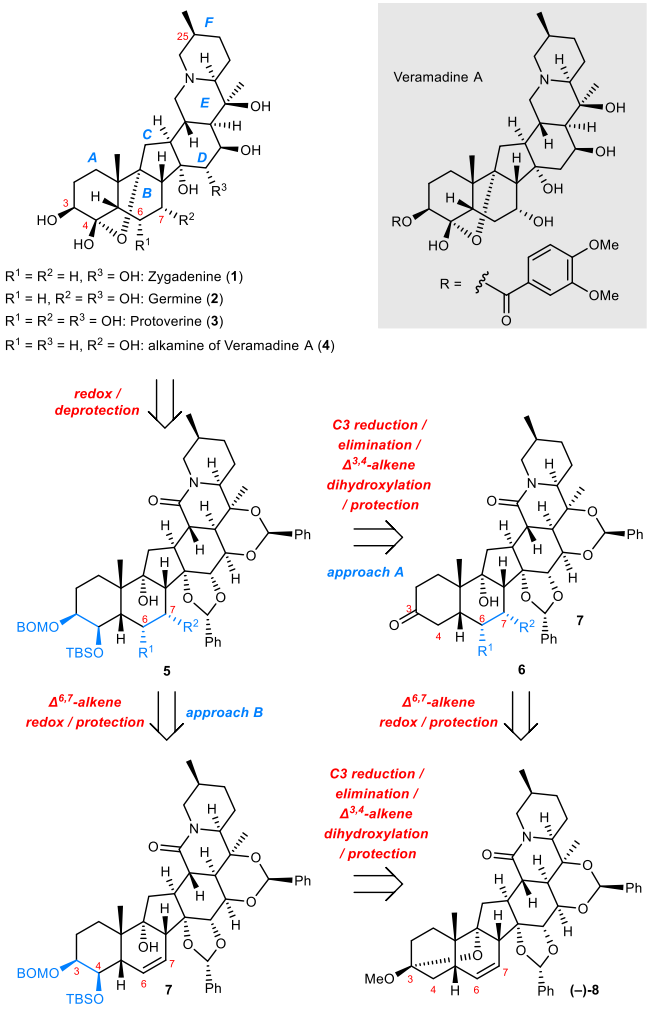

Fig. 2 | Retrosynthetic analysis of complex *Veratrum* alkaloids. The structure of veramadine A was highlighted in light gray background.

However, total syntheses of highly oxidized cevanine subtype alkaloids have remained limited. An important contribution in this context was made by Stork's group[26], where they successfully synthesized (±)−4-methylenegermine, which features only one additional methylene group compared to germine.

Zygadenine (**1**), germine (**2**) and protoverine (**3**) are highly oxidized members of the cevanine subgroup and serve as core alkamines for various natural products that exist as esters or polyesters of their hydroxyl groups, including germemine[27], neogermitrine[28], germitetrine[29], and protoveratrines[30]. Several of these alkaloids were previously used clinically for hypertension management[9]. However, due to adverse reactions such as neurotoxicity, safer alternatives have since replaced them[10]. Nevertheless, compounds **1, 2** and **3**, distinguished by increasing oxidation levels and multiple hydroxyl groups intricately embedded in the A-E rings, present opportunities for strategic innovation in accessing *Veratrum* alkaloids. In our prior work, we employed an intramolecular Diels–Alder reaction/radical cyclization strategy to construct the hexacyclic carbon skeleton, followed by a meticulously designed sequence of redox manipulations to complete the total synthesis of (−)-zygadenine (**1**)[31]. Herein, we unveil a late-stage neighboring group participation strategy, resulting in a divergent and enantioselective total synthesis of zygadenine (**1**), germine (**2**), protoverine (**3**), and the alkamine of veramadine A (**4**)[30].

Results and discussion

Retrosynthetic design

By analyzing the differences in these target molecules, we envisioned a divergent synthetic strategy and logically traced them back to intermediate **5** (Fig. 2). Starting from compound **8** communicated in our previous publication[31], hydrogenation of the Δ[6,7]-alkene followed by subsequent redox and protection/deprotection manipulations could transform it into zygadenine (**1**). In comparison, for germine (**2**), protoverine (**3**), and the alkamine of veramadine A (**4**), the installation of the C6 and/or C7 hydroxyl groups must be achieved in a regio- and stereoselective manner, alongside the introduction of the C3 and C4 oxidation states. Tactically, the functionalization of

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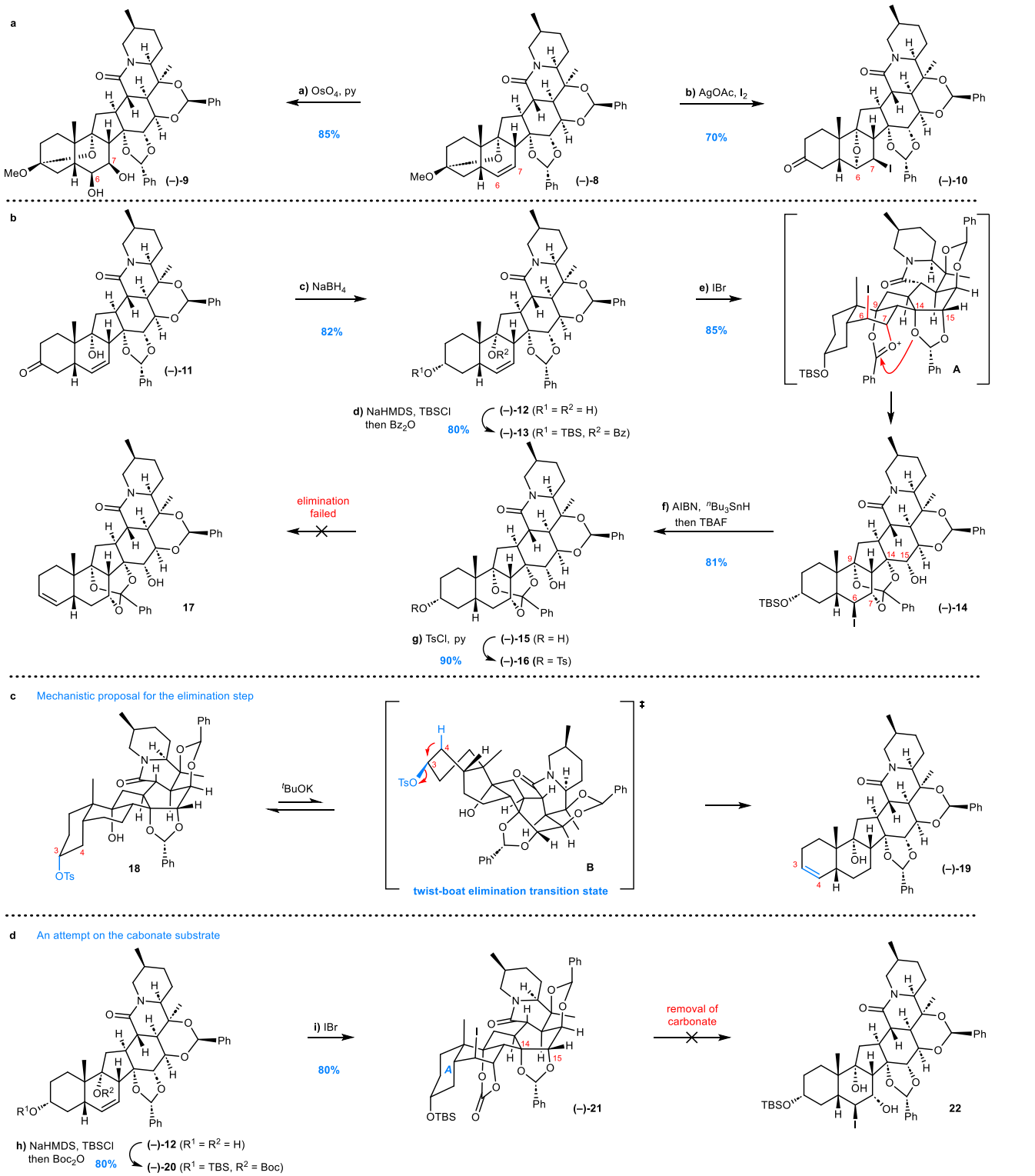

Fig. 3 | Evolution of strategies to functionalize the $\Delta^{6,7}$-alkene. a Attempted dihydroxylation of the $\Delta^{6,7}$-alkene. **b** Initial exploration of the neighboring-group participation strategy. **c** Analysis of the successful elimination reaction in **18**. **d** The failed attempt to access the substrate with free C9-OH via a carbonate intermediate. Reagents and conditions: (**a**) OsO_4, pyridine, 0 °C to rt, overnight, 85%. **b** AgOAc, I_2, AcOH, overnight, 70%. **c** $NaBH_4$, DCM/MeOH=1:4, 0 °C, 30 min, 82%. **d** NaHMDS, TBSCl, then Bz_2O, THF, 0 °C, 1 h, 80%. **e** IBr, MeCN, buffer (pH = 7), 28 °C, 2 h, 85%. **f** AIBN, $^nBu_3SnH$, benzene, reflux, 1 h then TBAF, THF, rt, 2 h, 81%. **g** TsCl, pyridine, rt, 5 h, 90%. **h** NaHMDS, TBSCl, then Boc_2O, THF, 0 °C, 1 h, 80%. **i** IBr, MeCN, buffer (pH = 7), 28 °C, 2 h, 80%.

the $\Delta^{6,7}$-alkene could proceed before the C3 reduction, regioselective elimination, dihydroxylation, and subsequent stepwise protections that install the protected hydroxyl groups at C3 and C4 (approach A), and intermediate **6** was hence devised. Alternatively, the protected hydroxyl groups at C3 and C4 could be secured first, followed by the functionalization of the $\Delta^{6,7}$-alkene (via **7**, approach B). Either way, the challenges associated with the chemo-, regio-, and stereochemical selectivity of late-stage transformations in a complicated polycyclic

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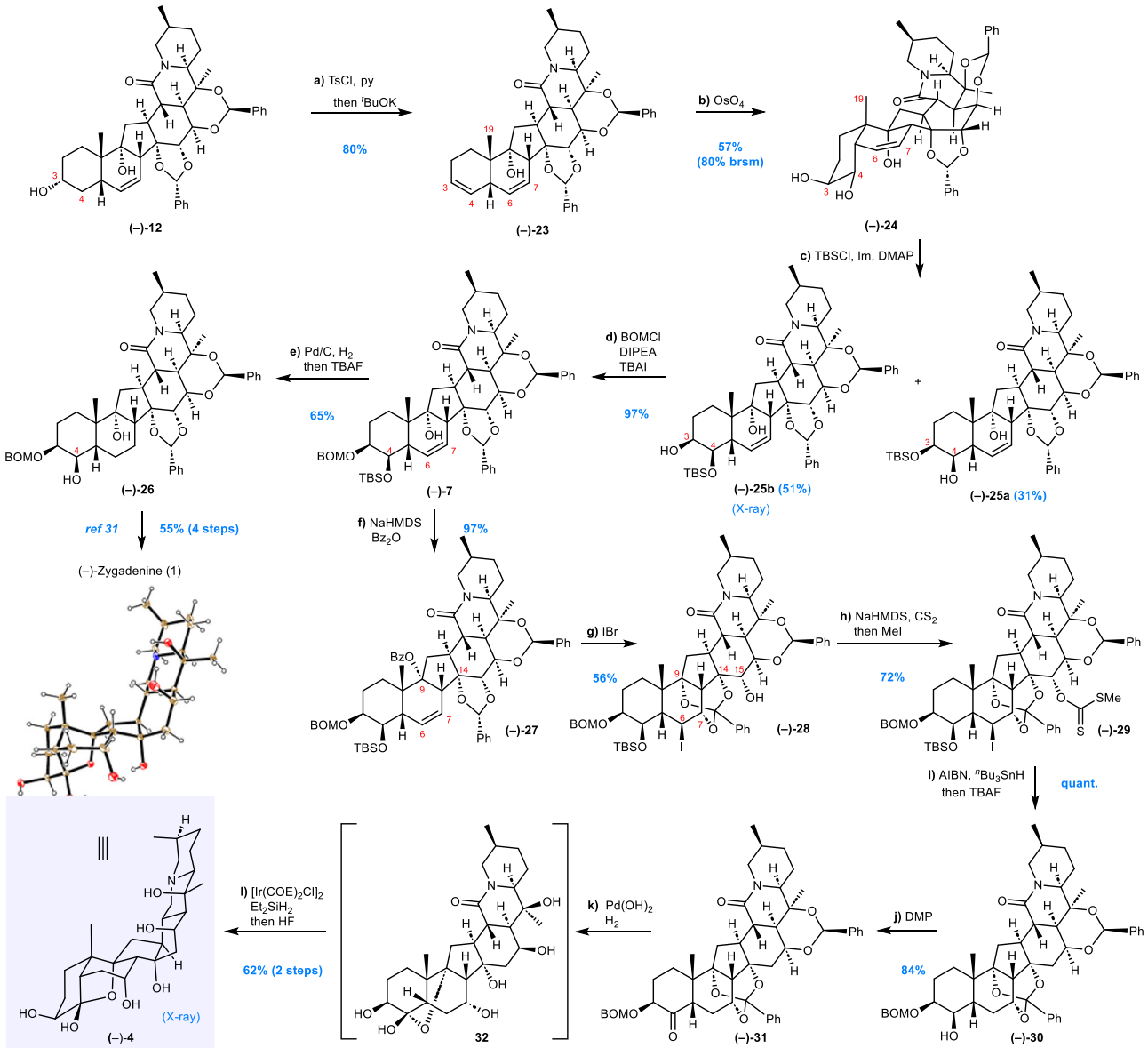

Fig. 4 | Formal synthesis of (−)-zygadenine (1) and synthesis of the alkamine of veramadine A (−)-4. Reagents and conditions: **a** TsCl, pyridine, 50 °C, 2 h then ^{t}BuOK, toluene, DMSO, −78 °C to −25 °C, 30 min, 80%. **b** OsO_4, pyridine, THF, −40 °C, 2 h, 57% (80% brsm). **c** TBSCl, imidazole, DMAP, DCM, rt, overnight, 82% (**68a**/**68b** = 3:5) **d** BOMCl, DIPEA, TBAI, DCE, 80 °C, 1 h, 97%. **e** Pd/C, EtOAc, Et_3N, H_2 (7 MPa), rt, 20 h then TBAF, THF, 70 °C, 5 h, 65%. **f** NaHMDS, Bz_2O, THF, 0 °C, 1 h, 97%. **g** IBr, MeCN, buffer (pH=7), 28 °C, 2 h, 56%. **h** NaHMDS, CS_2, THF, −78 °C, 10 min then MeI, −78 °C, 30 min, 72%. **i** AIBN, $^{n}Bu_3SnH$, benzene, reflux, 1.5 h then TBAF, THF, reflux, 3 h, quant. **j** DMP, $NaHCO_3$, DCM, rt, 15 h, 84%. **k** $Pd(OH)_2$/C, MeOH, H_2 (1 atm), rt, 5 h. **l** Et_2SiH_2, $[Ir(COE)_2Cl]_2$, toluene, reflux, 3 h then MeCN, HF (40% aq.), rt, overnight, 62% (2 steps). brsm, yield based on the recovered starting material; BOMCl, Benzyl chloromethyl ether; DMP, Dess-Martin periodinane.

skeleton should not be underestimated, and significant experimentation was anticipated to achieve the desired results.

Implementation of a late-stage neighboring-group participation to functionalize the $\Delta^{6,7}$-alkene

We commenced by adjusting the oxidation states of C6 and C7 through transformations of the $\Delta^{6,7}$-alkene moiety within the *cis*-decahydronaphthalene framework of **8**. Initially, a direct oxidation strategy was employed (Fig. 3a). However, dihydroxylation of **8** with OsO_4 resulted in diol **9** with incorrect stereochemistry at C6 and C7, likely due to significant steric hindrance on the α surface in the AB-ring system. Evaluating Woodward *cis*-hydroxylation conditions (AgOAc, I_2) on **8** revealed a side reaction involving the nucleophilic attack of the C9-OH on the iodonium intermediate[32], yielding the undesired product **10**.

These initial endeavors sparked the investigation of a neighboring-group participation strategy by leveraging the C9-OH group (Fig. 3b). Reduction of **11**[31] by $NaBH_4$, which approached the C3 carbonyl group from the convex face, gave **12** in 82% yield as a single isomer. Protection of the C3-OH in **12** using TBS, followed by benzoylation of the C9-OH in a one-pot procedure, provided **13** in 80% yield. Notably, this method (NaHMDS/Bz_2O) exhibited remarkable efficiency for the acylation of the C9-OH, representing a rare example of benzoylation on a tertiary hydroxyl group despite the considerable steric hinderance. Treatment of **13** with IBr afforded orthoester **14** in 85% yield. This cascade event proceeded via oxocarbenium intermediate **A**, which engaged the neighboring oxygen at the C14 position to form the orthoester, leading to the selective deprotection of the C14, C15-benzylidene acetal. With the correct oxidation level and configuration at C7 successfully attained, we employed radical

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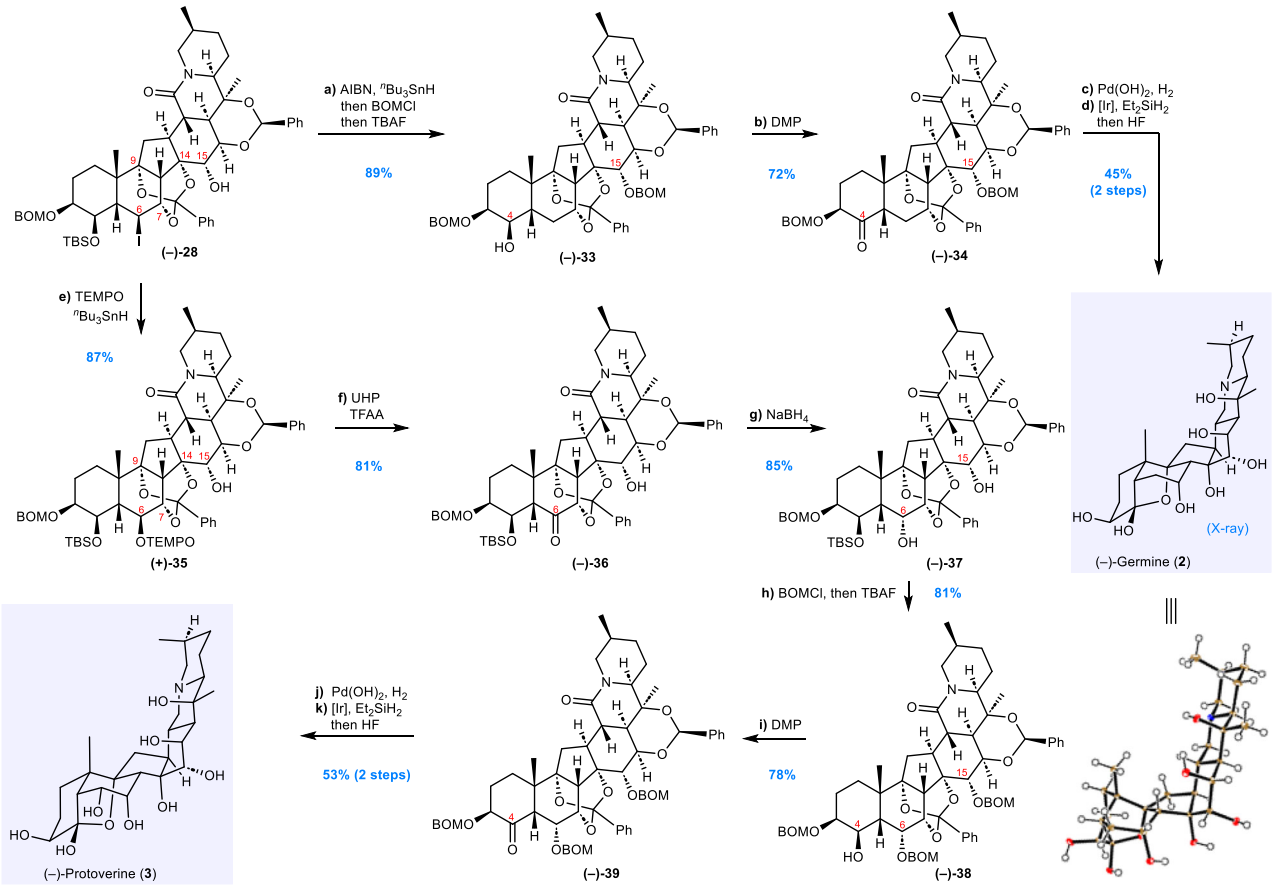

Fig. 5 | Syntheses of (−)-germine (2) and (−)-protoverine (3). Reagents and conditions: **a** $^{n}Bu_3SnH$, AIBN, benzene, reflux, 1.5 h then BOMCl, TBAI, DIPEA, DCE, 80 °C, 2 h then TBAF, THF, reflux, 3 h, 89%. **b** DMP, $NaHCO_3$, DCM, 30 °C, 13 h, 72%. **c** $Pd(OH)_2/C$, MeOH, H_2 (1 atm), rt, 5 h. **d** Et_2SiH_2, $[Ir(COE)_2Cl]_2$, toluene, reflux, 3 h then MeCN, HF (40% aq.), rt, overnight, 45% (2 steps). **e** TEMPO, $^{n}Bu_3SnH$, toluene, reflux, 3 h, 87%. **f** UHP, Na_2CO_3, TFAA, DCM, 0 °C, 6 h, 81%. **g** $NaBH_4$, MeOH, 0 °C, 30 min, 85%. **h** BOMCl, TBAI, DIPEA, DCE, 80 °C, 2 h, then TBAF, THF, reflux, 3 h, 81%. **i** DMP, $NaHCO_3$, DCM, 30 °C, 14 h, 78%. **j** $Pd(OH)_2/C$, MeOH, H_2 (1 atm), rt, 5 h. **k** Et_2SiH_2, $[Ir(COE)_2Cl]_2$, toluene, reflux, 3 h then MeCN, HF (40% aq.), rt, overnight, 53% (2 steps). UHP, urea hydrogen peroxide; TFAA, trifluoroacetic anhydride.

dehalogenation of the C-6 iodide and deprotected the TBS group to yield **15**. We then examined the elimination/dihydroxylation strategy for introducing the C4 oxidation state. However, after tosylation of the C3-OH, the elimination did not occur upon treatment with ^{t}BuOK, resulting in the recovery of tosylate **16**.

This experimental observation prompted a careful assessment of the mechanism underlying the elimination of C3-OTs. The elimination in substrate **18** to form the $\Delta^{3,4}$-alkene could be realized, as communicated in our former publication[31]. A plausible explanation is that the elimination reaction to form the $\Delta^{3,4}$-alkene requires C3–OTs and C4-β-H to be *trans*-coplanar, necessitating the A-ring to adopt a twist-boat conformation (**B**, Fig. 3c). This conformation can occur in substrate **18**. However, in substrate **16**, the B-ring conformation was locked by the orthoester structure, adding extra conformational constraints in the AB ring system, and making it difficult to achieve the necessary conformation in the A-ring for the *trans*-elimination. Therefore, we opted to protect the C9–OH with a Boc group, yielding intermediate **20**, which was then treated with IBr to afford **21** in 80% yield (Fig. 3d). We then attempted to deprotect the C9–OH to release the conformational constraint in the AB system to ensure the elimination reaction. However, removing the carbonate group via alkaline hydrolysis proved challenging. Instead of obtaining **22** or the corresponding epoxide, we observed the recovery of starting material **21**, indicating significant steric hinderance near the carbonate, likely due to the A-ring and the benzylidene acetal on C14,C15-diol.

Total syntheses of (−)-zygadenine, (−)-germine, (−)-protoverine, and the alkamine of veramadine A

Subsequently, the reaction sequence was modified so that the neighboring-group participation reaction occurred after the elimination/dihydroxylation of the C3-C4 position (Fig. 4). Initially, compound **12** underwent the elimination of the C3-OH through tosylation and treatment with ^{t}BuOK, leading to the formation of the $\Delta^{3,4}$-alkene product in 20% yield, which was contaminated by $\Delta^{2,3}$-alkene and $\Delta^{4,5}$-alkene byproduct. After screening conditions, we were able to regio-selectively obtain the desired $\Delta^{3,4}$-alkene product (**23**) in 80% isolated yield by controlling the reaction temperature to −25 °C and adding ^{t}BuOK solid slowly in batches. Next, we attempted the regio- and facial-selective dihydroxylation of the $\Delta^{3,4}$-alkene of **23**. Under OsO_4/pyridine treatment, the desired product **21** was obtained in only 13% yield, along with byproducts from dihydroxylation of the $\Delta^{6,7}$-alkene and both the $\Delta^{3,4}$-alkene and $\Delta^{6,7}$-alkene. After careful optimization, the regioselective product **24** was obtained in 57% yield (80% brsm) by dropwisely adding the OsO_4 solution at low temperature. Mono-protection with TBS provided separable regioisomers **25a** and **25b** in 31% and 51% yields, respectively, with the undesired regioisomer (**25a**) being recyclable. Intermediate **25b** was further converted to **7**, the late-stage common intermediate for our total synthesis endeavor, by installing a BOM protecting group on the C3–OH. For the synthesis of (−)-zygadenine (**1**), the C6–C7 alkene was hydrogenated, and the C4–OH was deprotected via TBAF treatment in a one-pot fashion,

resulting in the intermediate **26**, which could be directed towards (−)-**1** using identical reaction sequences in our previous publication[31].

We then proceeded to diverge from **7** to obtain **2, 3** and **4**. The alkamine of veramadine A (**4**)[30], a congener with the same oxidation level as zygadenine (**1**), was targeted first. A benzoyl group was introduced to the C9-OH to give **27**, and subsequent IBr treatment afforded orthoester **28** in 56% yield. Conversion of the C15–OH to the corresponding xanthate **29** was followed by radical defunctionalization to adjust the oxidation levels at C6 and C15, and one-pot TBAF treatment afforded alcohol **30**. The C4-OH group was then oxidized to a ketone to give **31** in 84% yield, and global deprotection via palladium-catalyzed hydrogenation released the C9-OH to form the hemiketal (**32**), serving as protection of the C4-ketone during iridium-catalyzed silane-reduction[33]. Notably, silylation of the hydroxyl groups occurred during this final transformation; therefore, hydrofluoric acid treatment was performed in the same reaction flask after the reduction, leading to the isolation of the alkamine of veramadine A (**4**) in 62% yield over two steps.

To access germine (**2**), radical dehalogenation of the iodide in **28** was followed by protecting the C15-OH group with a BOM group, and TBAF treatment was performed in a one-pot fashion to yield **33** (Fig. 5). This was followed by DMP oxidation of the C4-OH group to deliver ketone **34**. Sequential global deprotection and final amide reduction then afforded (−)-germine (**2**) in 45% yield over two steps. The elaboration of **28** to protoverine (**3**) commenced with the transformation of C6-I to a TEMPO group, resulting in **35** using Boger's protocol[34]. Subsequent peroxy acid oxidation produced the C6 ketone **36**, which was then reduced by $NaBH_4$ to introduce the β-C6-OH group, yielding **37**. Intermediate **37** underwent BOM protection of both the C6 and C15 hydroxyl groups, followed by desilylation of the TBS-protected C4−OH group, leading to the formation of **38**. A subsequent DMP oxidation step resulted in ketone **39** in 78% yield. The final steps involved the same global deprotection and amide reduction sequence as previously utilized for **4**, culminating in the total synthesis of (−)-protoverine (**3**). The NMR spectra of the synthesized samples of **2** were consistent with those reported in the literature (Supplementary Table 2)[30,35], while the structures of **2** and **4** were unambiguously verified by X-ray diffraction analysis; the stereochemistry of **3** was determined through 2D NMR experiments due to the unavailability of NMR spectra data of the isolated sample.

In summary, we have developed a successful divergent approach for the syntheses of (−)-zygadenine (**1**), (−)-germine (**2**), (−)-protoverine (**3**) and the alkamine of veramadine A (**4**). The primary challenge lay in achieving chemo-, regio- and stereoselectivity during the late-stage transformations, especially redox sequence, within this complex and highly oxidized framework. Ultimately, the functionalization of the C6-C7 alkene using neighboring-group participation (C9-OBz) after the introduction of the protected C4-OH proved to be an essential tactic. This synthetic strategy not only provides a pathway to access other important members of the *Veratrum* family of alkaloids but also offers opportunities for further exploration of their pharmacological properties.

Methods

Unless otherwise mentioned, all reactions were carried out under a nitrogen atmosphere with dry solvents under anhydrous conditions. All the chemicals were purchased commercially, and used without further purification. Anhydrous THF was distilled from sodium-benzophenone, toluene was distilled from sodium, dichloroethane and dichloromethane were distilled from calcium hydride according to Purification of Laboratory Chemicals (Peerrin, D. D.; Armarego, W. L. and Perrins, D. R., Pergamon Press: Oxford, 1980). Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm E. Merck silica plates (60F-254), using UV light as the visualizing agent and an ethanolic solution of ammonium molybdate and heat, or $KMnO_4$ and heat as developing agents. If not specially mentioned, flash column chromatography uses silica gel (200–300 mesh) supplied by Tsingtao Haiyang Chemicals (China). NMR spectra were recorded on Brüker Advance 400 (^{1}H 400 MHz, ^{13}C 100 MHz), Brüker Advance 500 (^{1}H 500 MHz, ^{13}C 125 MHz), Brüker Advance 600 (^{1}H 600 MHz, ^{13}C 150 MHz) or Brüker Advance 800 (^{1}H 800 MHz, ^{13}C 200 MHz). TMS was used as internal standard for ^{1}H NMR (0.00 ppm), and solvent signal was used as reference for ^{1}H NMR ($CDCl_3$, 7.26 ppm, CD_2Cl_2, 5.32 ppm, CD_3OD, 3.31 ppm, CD_3COCD_3, 2.05 ppm, C_6D_6, 7.16 ppm), ^{13}C NMR ($CDCl_3$, 77.16 ppm, CD_2Cl_2, 54.0 ppm, CD_3OD, 49.00 ppm, CD_3COCD_3, 206.26, 29.84 ppm, C_6D_6, 128.06 ppm). The following abbreviations were used to explain the multiplicities: *s* = singlet, *d* = doublet, *t* = triplet, *q* = quartet, *m* = multiplet, *br* = broad. Mass spectrometric data were obtained using Brüker Apex IV FTMS using ESI (electrospray ionization) and Waters GCT (GC-MS) using EI (electron impact ionization). Infrared spectra were recorded on a Thermo Nicolet iS5 spectrometer. Optical rotations were measured on an InsMark IP-digi300 digital polarimeter with a LED light source at ambient temperature and are reported as follows: $[\alpha]^{\lambda}$ (c g/100 mL).

Data availability

The additional data generated in this study are provided in the Supplementary Information. The X-ray crystallographic for the structures reported in this study have been deposited at the Cambridge Crystallographic Data Center (CCDC), under deposition numbers CCDC 2278629 (**25b**), CCDC 2278631 (**4**) and CCDC 2278630 (**2**). Copies of the data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures/. (also see 'X-Ray Crystallographic Data' in Supplementary Information). All data are available from the corresponding author upon request.

References

1. Greenhill, J. V. & Grayshan, P. *The Cevane Group of Veratrum Alkaloids*; Academic Press: **41**, 177–252 (1992).
2. Heretsch, P. & Giannis, A. *The Veratrum and Solanum Alkaloids*; Academic Press: **74**, 201–232 (2015).
3. Dirks, M. L., Seale, J. T., Collins, J. M. & McDougal, O. M. Review: *Veratrum californicum* alkaloids. *Molecules* **26**, 5934–5953 (2021).
4. Incardona, J. P., Gaffield, W., Kapur, R. P. & Roelink, H. The teratogenic Veratrum alkaloid cyclopamine inhibits sonic hedgehog signal transduction. *Development* **125**, 3553–3562 (1998).
5. Chen, J. K., Taipale, J., Cooper, M. K. & Beachy, P. A. Inhibition of hedgehog signaling by direct binding of cyclopamine to smoothened. *Genes Dev.* **16**, 2743–2748 (2002).
6. Chen, J. I Only Have eye for ewe: the discovery of cyclopamine and development of hedgehog pathway-targeting drugs. *Nat. Prod. Rep.* **33**, 595–601 (2016).
7. Budzikiewicz, H. Zum massenspektroskopischen fragmentierungsverhalten von steroidalalkaloiden. *Tetrahedron* **20**, 2267–2278 (1964).
8. Gilbertson, T. J. Zygacine and zygadenine: the major alkaloids from *Zygadenus gramineus*. *Phytochemistry* **12**, 2079–2080 (1973).
9. Meilman, E. The management of hypertensive cardiovascular disease. *Circulation* **13**, 596–607 (1956).
10. Zhao, Y. et al. Research development towards the pharmacology and toxicology of *Veratrum* alkaloids. *Tradit. Chin. Drug Res. Clin. Pharmacol.* **19**, 240–242 (2008).
11. Zhang, X.-y, Bi, R.-y, Zhang, P. & Gan, Y.-h Vetradine modifies the gating of human voltage-gated sodium channel Nav1.7. *Acta Pharmacol. Sin.* **39**, 1716–1724 (2018).
12. Craig, R. A., Garrison, C. E., Nguyen, P. T., Yarov-Yarovoy, V. & Du Bois, J. Veratridine: a Janus-faced modulator of voltage-gated sodium ion channels. *Acs. Chem. Neurosci.* **11**, 418–426 (2020).
13. Gulsevein, A. et al. Veratridine can bind to a site at the mouth of the channel pore at human cardiac sodium channel $Na_V1.5$. *Int. J. Mol. Sci.* **23**, 2225 (2022).

14. Masamune, T., Takasugi, M., Murai, A. & Kobayashi, K. C-*Nor*-D-*homo* steroids and related alkaloids. IX. Synthesis of jervine and related alkaloids. *J. Am. Chem. Soc.* **89**, 4521–4523 (1967).
15. Johnson, W. S., DeJongh, H. A. P., Coverdale, C. E., Scott, J. W. & Burckhardt, U. Synthesis of veratramine. *J. Am. Chem. Soc.* **89**, 4523–4524 (1967).
16. Johnson, W. S., Cox, J. M., Graham, D. W. & Whitlock, H. W. The total synthesis of 17-acetyl-5α-etiojerva-12,14,16-trien-3β-ol. *J. Am. Chem. Soc.* **89**, 4524–4526 (1967).
17. Kutney, J. P. et al. Total synthesis of steroidal derivatives. V. The total synthesis of *Veratrum* alkaloids. 1. verarine. *J. Am. Chem. Soc.* **90**, 5332–5334 (1968).
18. Kutney, J. P. et al. Synthetic studies in the *Veratrum* alkaloid series. The total synthesis of C_{18}-functionalized C-*nor*-D-*homo* steroid derivatives-valuable intermediates in the total synthesis of *Veratrum* alkaloids. *J. Am. Chem. Soc.* **99**, 963–964 (1977).
19. Kutney, J. P. et al. Synthetic studies in the *Veratrum* alkaloid series. The total synthesis of verticine. *J. Am. Chem. Soc.* **99**, 964–966 (1977).
20. Giannis, A., Heretsch, P., Sarli, V. & Stößel, A. Synthesis of cyclopamine using a biomimetic and diastereoselective approach. *Angew. Chem., Int. Ed.* **48**, 7911–7914 (2009).
21. Sofiadis, M. et al. Convergent total synthesis of (–)-cyclopamine. *J. Am. Chem. Soc.* **145**, 21760–21765 (2023).
22. Shao, H. et al. Asymmetric synthesis of cyclopamine, a hedgehog (Hh) signaling pathway inhibitor. *J. Am. Chem. Soc.* **145**, 25086–25092 (2023).
23. Hou, W. et al. Divergent and gram-scale syntheses of (–)-veratramine and (–)-cyclopamine. *Nat. Commun.* **15**, 5332 (2024).
24. Cassaidy, K. J. & Rawal, V. H. Enantioselective total synthesis of (+)-heilonine. *J. Am. Chem. Soc.* **143**, 16394–16400 (2021).
25. Jin, Y., Hok, S., Bacsa, J. & Dai, M. Convergent and efficient total synthesis of (+)-heilonine enabled by C–H functionalizations. *J. Am. Chem. Soc.* **146**, 1825–1831 (2024).
26. Stork, G. et al. Synthetic study toward total synthesis of (±)–4-methylenegermine. *Org. Lett.* **19**, 5150–5153 (2017).
27. Kupchan, S. M. & Narayanan, C. R. Veratrum alkaloids. XXVIII. The structure and configuration of germine. *J. Am. Chem. Soc.* **81**, 1913–1921 (1959).
28. Kupchan, S. M. et al. Veratrum alkaloids. XXXVIII. The structure and configuration of protoverine. *J. Am. Chem. Soc.* **82**, 2242–2251 (1960).
29. Tang, J. et al. Four new germine esters from *Veratrum dahuricum*. *Helv. Chim. Acta* **90**, 769–775 (2007).
30. Tanaka, N., Suto, S. & Kobayashi, J. Veramadines A and B, new steroidal alkaloids from *veratrum maackii* var. *japonicum*. *Chem. Pharm. Bull.* **59**, 909–912 (2012).
31. Guo, Y. et al. Enantioselective total synthesis of (–)-zygadenine. *J. Am. Chem. Soc.* **145**, 20202–20207 (2023).
32. Woodward, R. B. & Brutcher, F. V. *cis*-Hydroxylation of a synthetic steroid intermediate with iodine, silver acetate and wet acetic acid. *J. Am. Chem. Soc.* **80**, 209–211 (1958).
33. Cheng, C. & Brookhart, M. Iridium-catalyzed reduction of secondary amides to secondary amines and imines by diethylsilane. *J. Am. Chem. Soc.* **134**, 11304–11307 (2012).
34. Boger, D. L. & McKie, J. A. An efficient synthesis of 1,2,9,9a-tetrahydrocyclopropa[c]benz[e]indol–4-one (CBI): an enhanced and simplified analog of the CC-1065 and duocarmycin alkylation subunits. *J. Org. Chem.* **60**, 1271–1275 (1995).
35. El Sayed, K. A., McChesney, J. D., Halim, A. F., Zaghloul, A. M. & Lee, I.-S. A study of alkaloids in *Veratrum viride* Aiton. *Pharm. Biol.* **34**, 161–173 (1996).

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Author contributions

The overall design of this project was conceptualized by Y.G. and T.L. with input from R.F., Y.J., and J.L.; Y.G., R.F., Y.J., J.L., and J.-T.L. conducted the chemical experiments. The manuscript was written and edited jointly by Y.G. and T. L. with feedback from other authors.

Competing interests

The other authors declare no competing interests.

Additional information

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