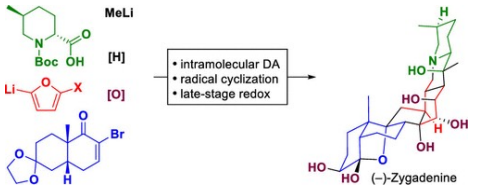
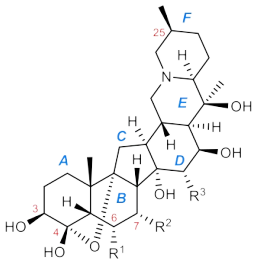
Divergent syntheses of complex Veratrum alkaloids

Yinliang Guo, Runting Fang, Yang Jiao, Jiaqi Liu, Jia-Tian Lu & Tuoping Luo
Nature Communications volume 15, Article number: 7639 (2024)

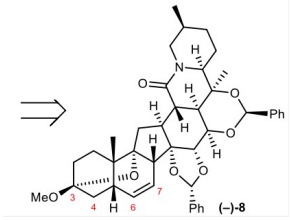


J. Am. Chem. Soc.

C-nor-D-homo steroid skeleton



$R^1 = R^2 = H$, $R^3 = OH$: Zygadenine (**1**)
$R^1 = H$, $R^2 = R^3 = OH$: Germine (**2**)
$R^1 = R^2 = R^3 = OH$: Protoverine (**3**)
$R^1 = R^3 = H$, $R^2 = OH$: alkamine of Veramadine A (**4**)



J. Am. Chem. Soc. 2023, 145, 37, 20202–20207

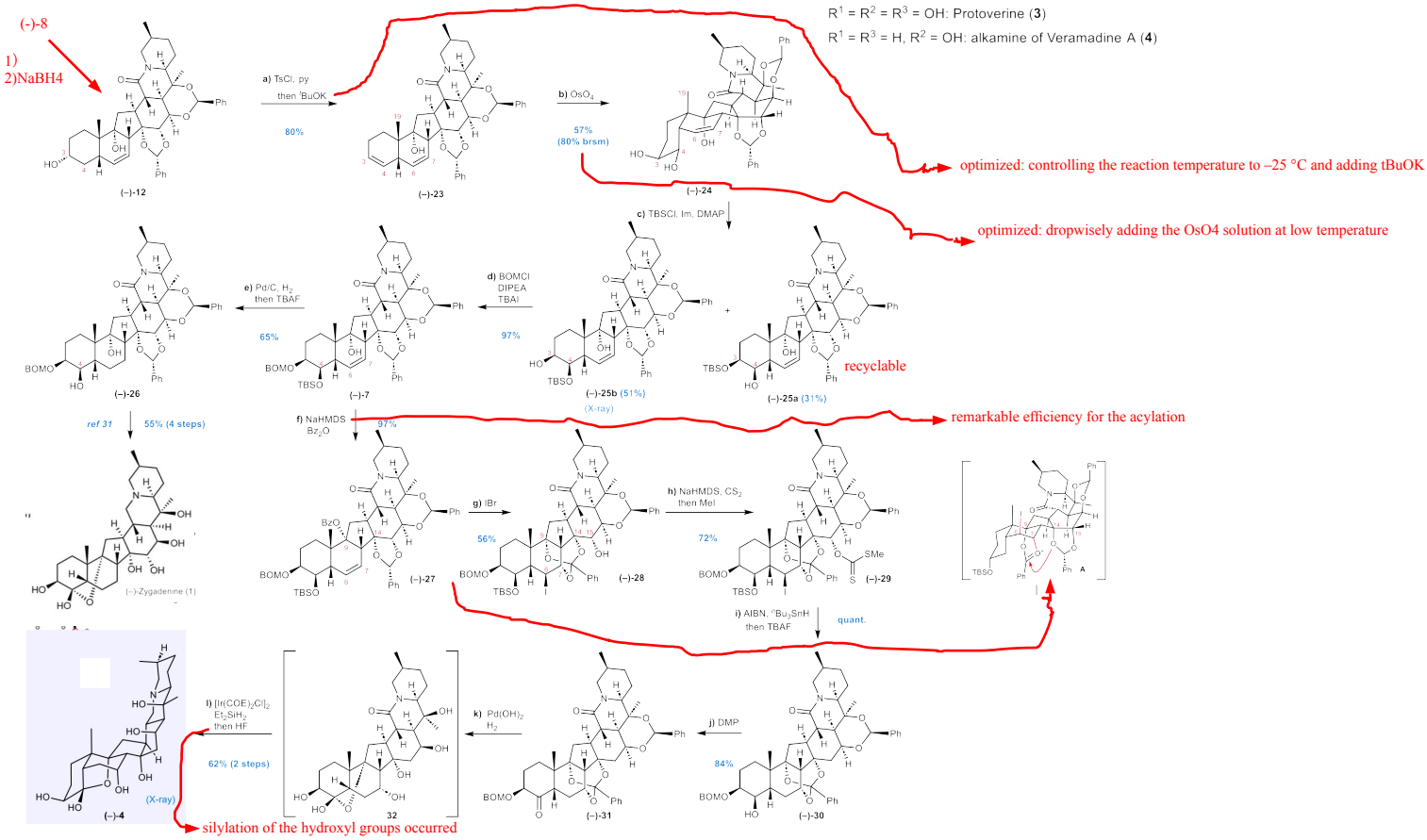
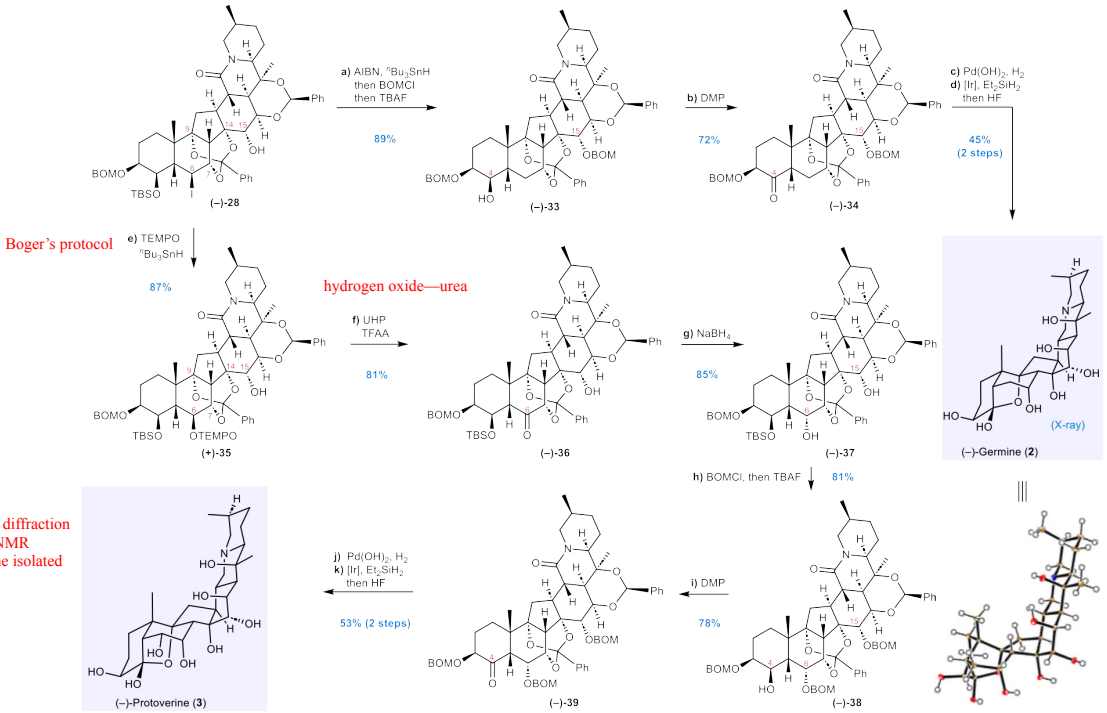


Fig. 4 | Formal synthesis of (−)-zygadenine (1) and synthesis of the alkamine of veramadine A (−)-4. Reagents and conditions: **a** TsCl, pyridine, 50 °C, 2 h then ^{t}BuOK, toluene, DMSO, −78 °C to −25 °C, 30 min, 80%. **b** OsO_4, pyridine, THF, −40 °C, 2 h, 57% (80% brsm). **c** TBSCl, imidazole, 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$_3$SnH, 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)$_2$Cl]$_2$, 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.



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

Fig. 5 | Syntheses of (−)-germine (2) and (−)-protoverine (3). Reagents and conditions: **a** ^{n}Bu$_3$SnH, 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)$_2$Cl]$_2$, toluene, reflux, 3 h then MeCN, HF (40% aq.), rt, overnight, 45% (2 steps). **e** TEMPO, ^{n}Bu$_3$SnH, 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)$_2$Cl]$_2$, toluene, reflux, 3 h then MeCN, HF (40% aq.), rt, overnight, 53% (2 steps). UHP, urea hydrogen peroxide; TFAA, trifluoroacetic anhydride.