A Ring-Deconstructive Carbon-Deletion Approach to the Enantioselective Total Synthesis of [5]-Ladderanoic Acid

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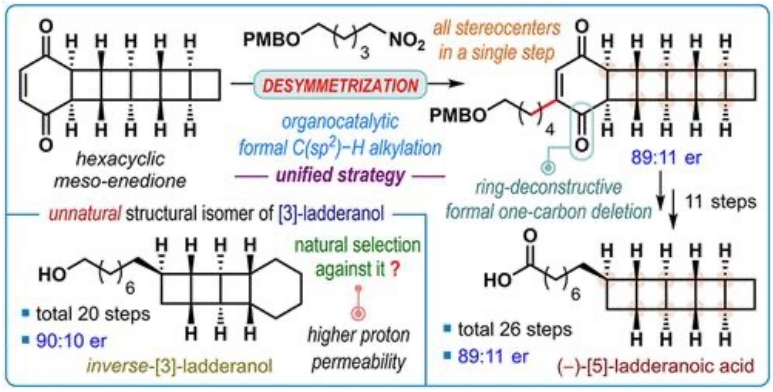
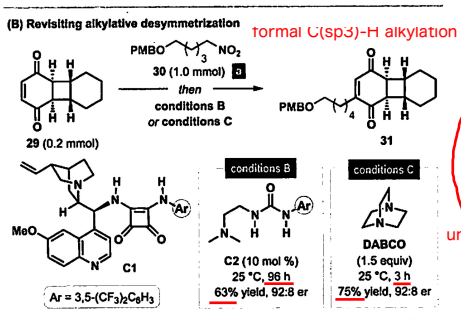
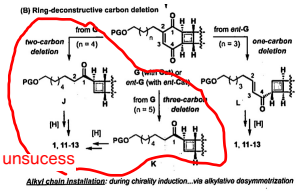
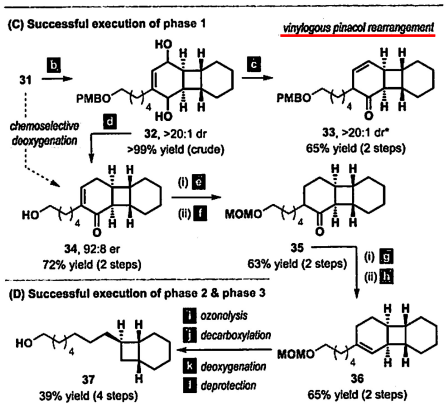




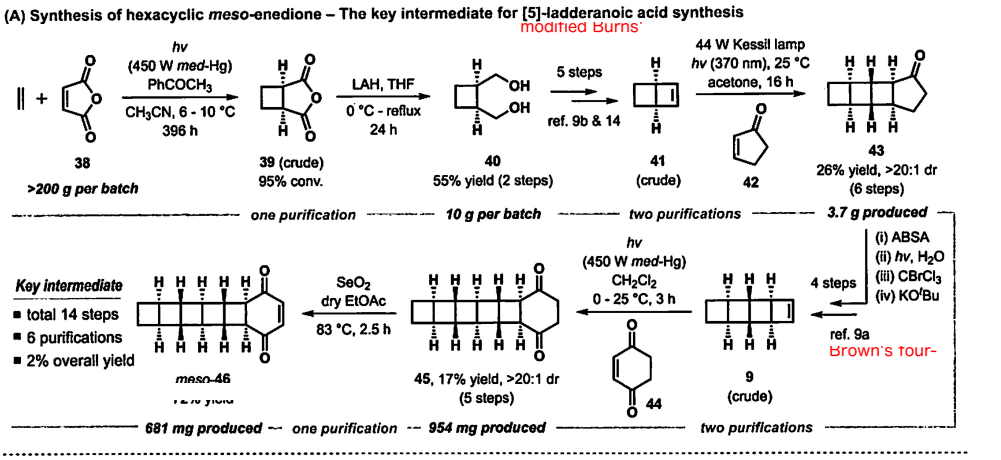


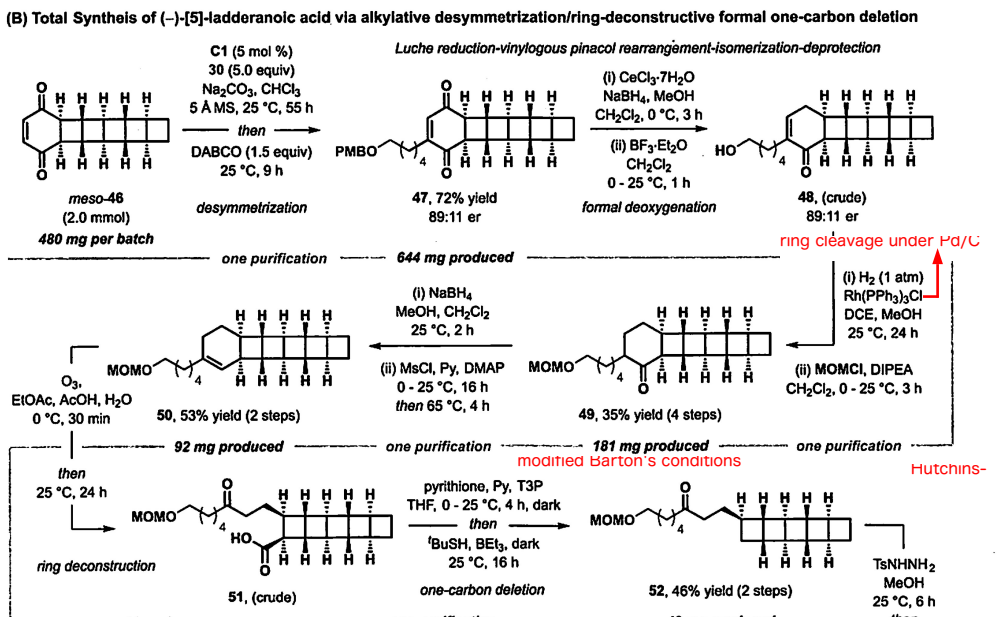


11 steps, 8% overall, five chromatographic purifications

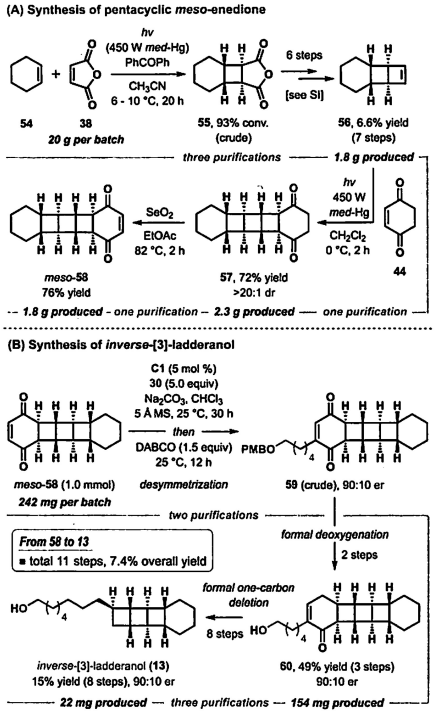
[a]Reagents and conditions: (a) **C1** (5 mol %), Na_2CO_3 (1.5 equiv), $CHCl_3$ (0.1 M), 5 Å MS, 25 °C, 30 h, then conditions A or B [Note: Unreacted nitroalkane **30** (0.76 mmol) was recovered and reused without any drop in efficiency of the reaction]; (b) $CeCl_3·7H_2O$, $NaBH_4$, MeOH, 0 °C, 2 h; (c) $BF_3·Et_2O$, THF, 25 °C, 30 min; (d) $BF_3·Et_2O$, CH_2Cl_2, 25 °C, 1 h; (e) H_2, 10% Pd/C (20 mol %), EtOAc, 25 °C, 3 h; (f) MOMCl, DIPEA, CH_2Cl_2, 0–25 °C, 16 h; (g) $NaBH_4$, MeOH/CH_2Cl_2 (3:1), 25 °C, 1 h; (h) MsCl, Py, DMAP, 0–25 °C, 16 h, then 65 °C, 3 h; (i) O_3, EtOAc/AcOH/H_2O (2:2:0.1), 0 °C, 30 min, then 25 °C, 16 h; (j) pyrithione, pyridine, T3P, THF, 4 h, dark, then ^tBuSH, BEt_3, 25 °C, 16 h, dark; (k) $TsNHNH_2$, MeOH, 25 °C, 6 h, then $NaBH_3CN$, $ZnCl_2$ in MeOH, 65 °C, 1 h, then (l) conc. HCl, 50 °C, 1 h (*one-pot*). *Diastereomeric ratio (dr) was determined from ^1H NMR of the crude reaction mixture.

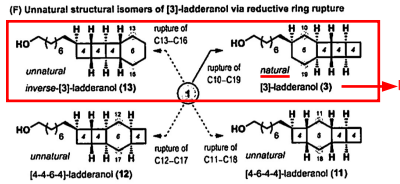
Scheme 6. Enantioselective Total Synthesis of (–)-[5]-Ladderanoic Acid through a Ring-Deconstructive Formal One-Carbon Deletion Strategy





Scheme 7. Enantioselective Synthesis of *Inverse*-[3]-ladderanol through a Ring-Deconstructive Formal One-Carbon Deletion Strategy





lower proton permeability across the membrane

the superiority of natural [3]-ladderanol over inverse-