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Total Synthesis of (−)-Lepenine

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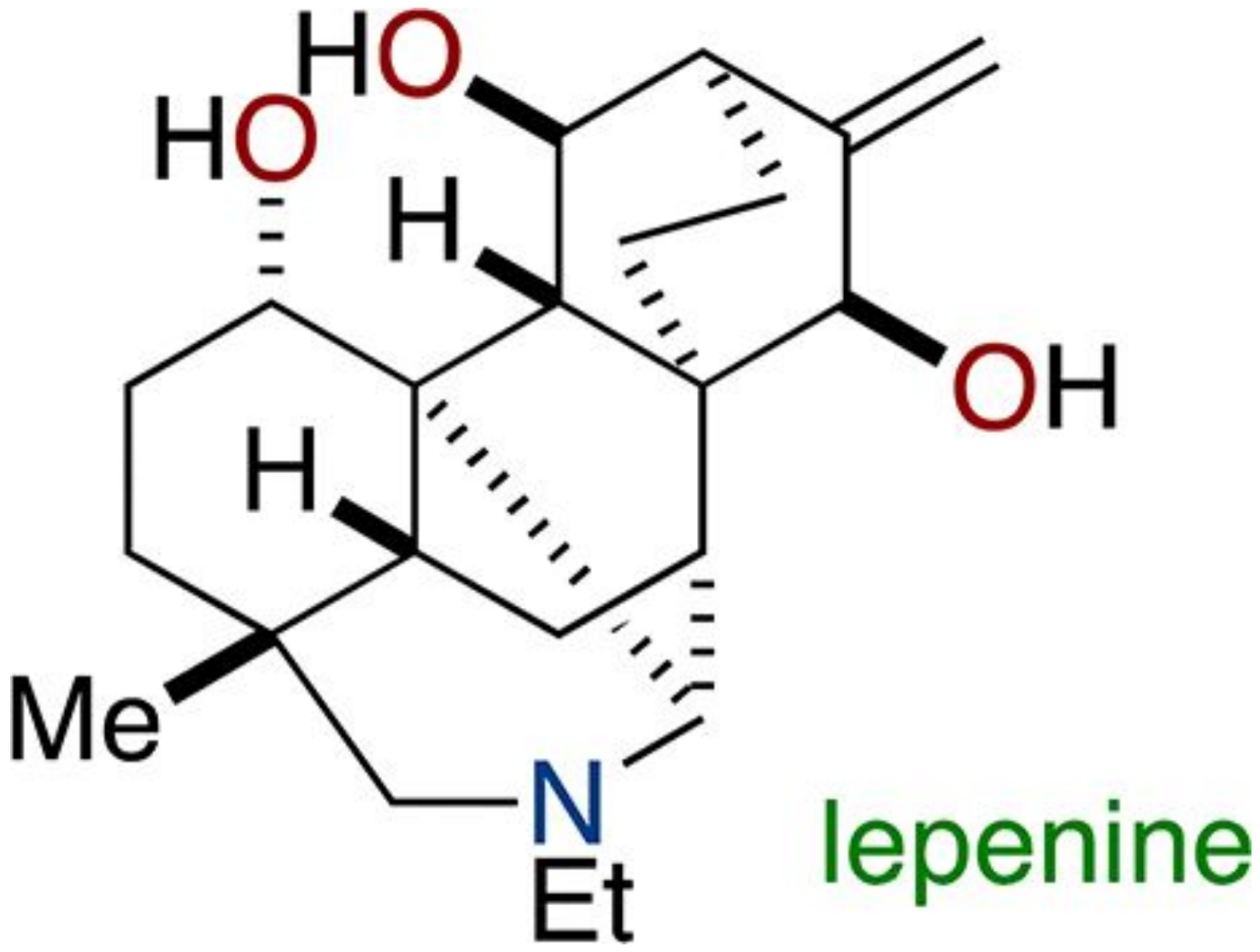
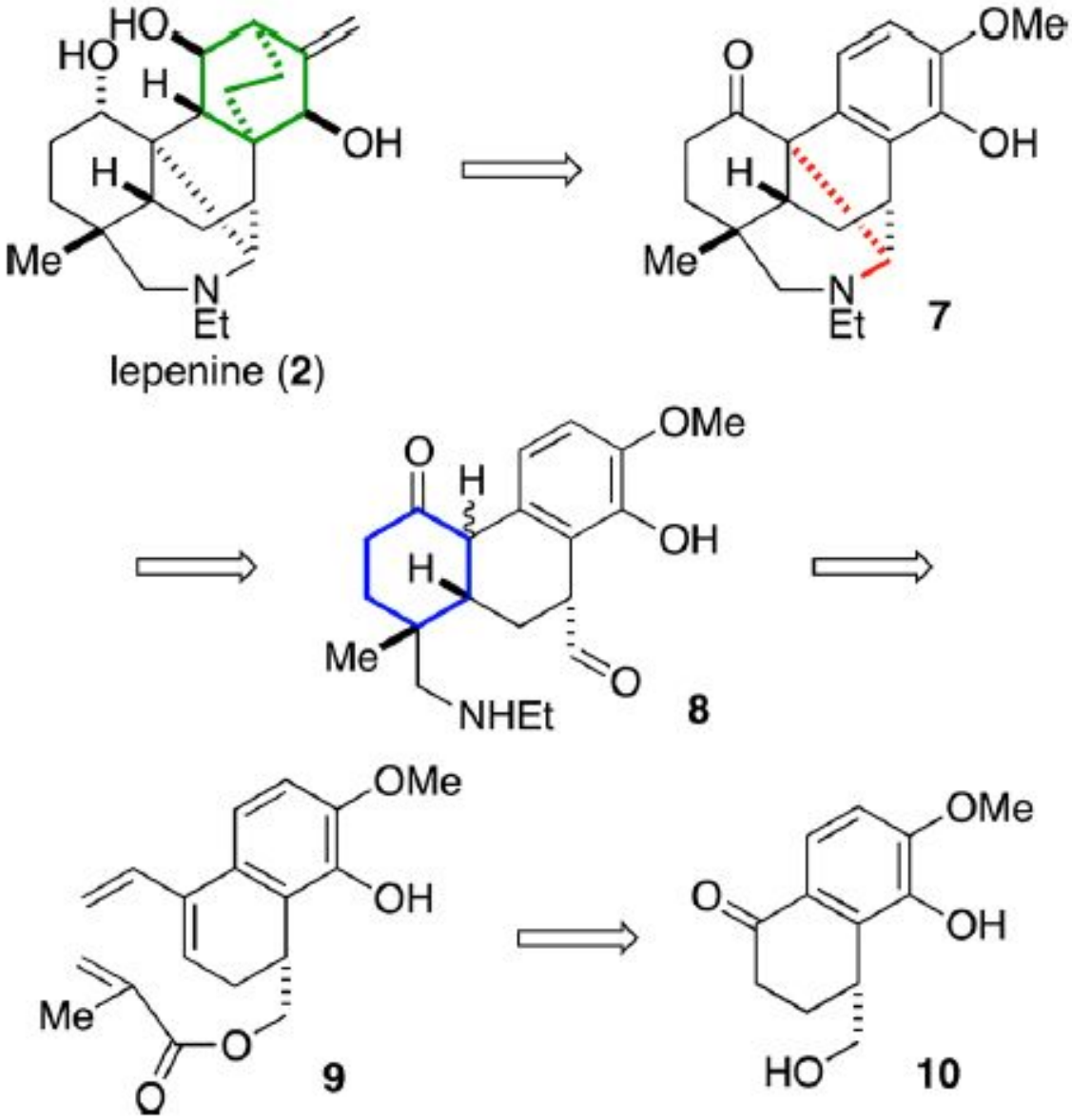
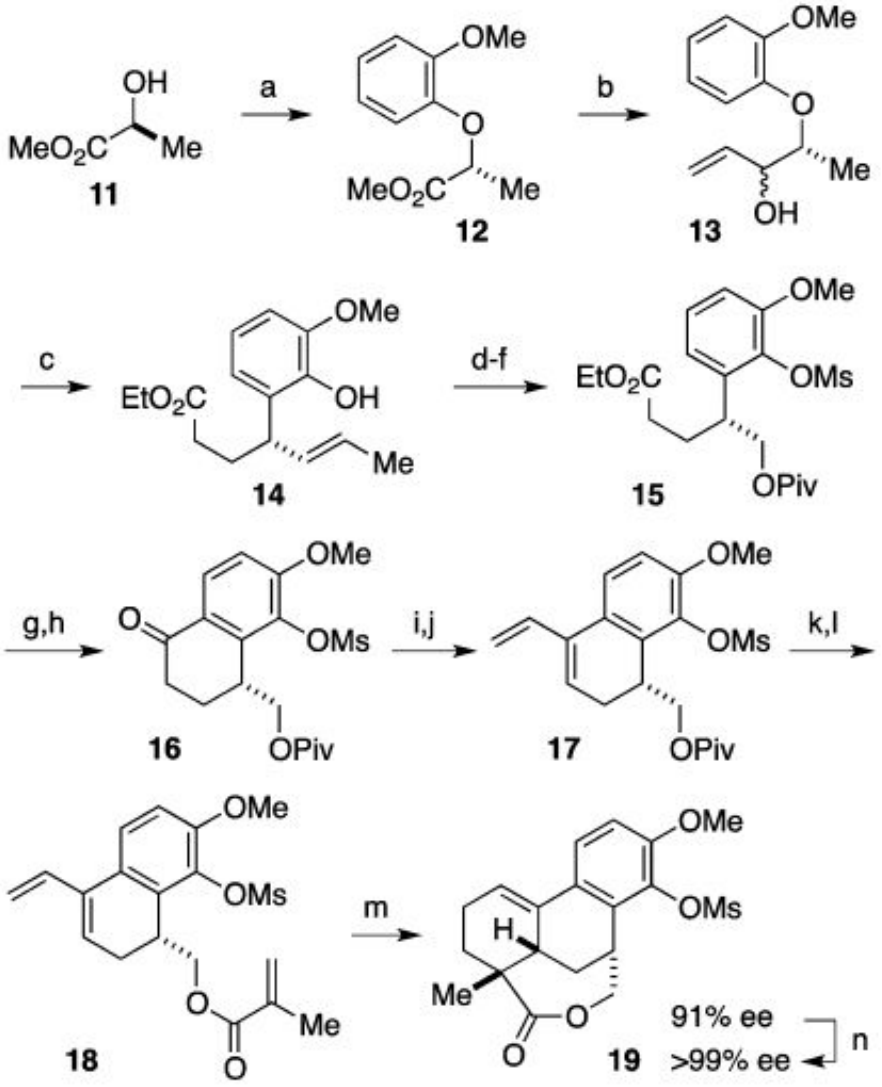


lepenine

Ретросинтетическая схема

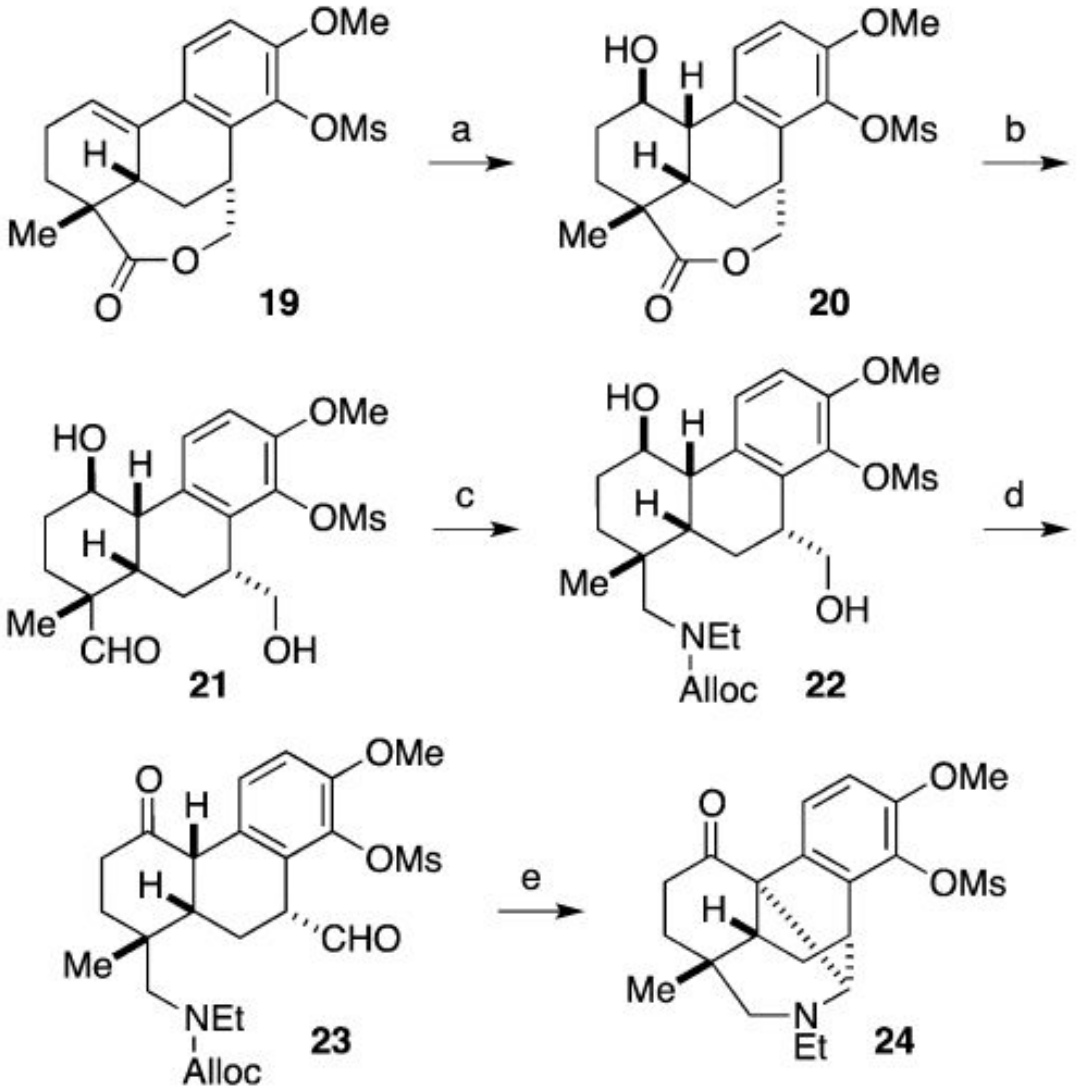


Синтез фенантренового каркаса



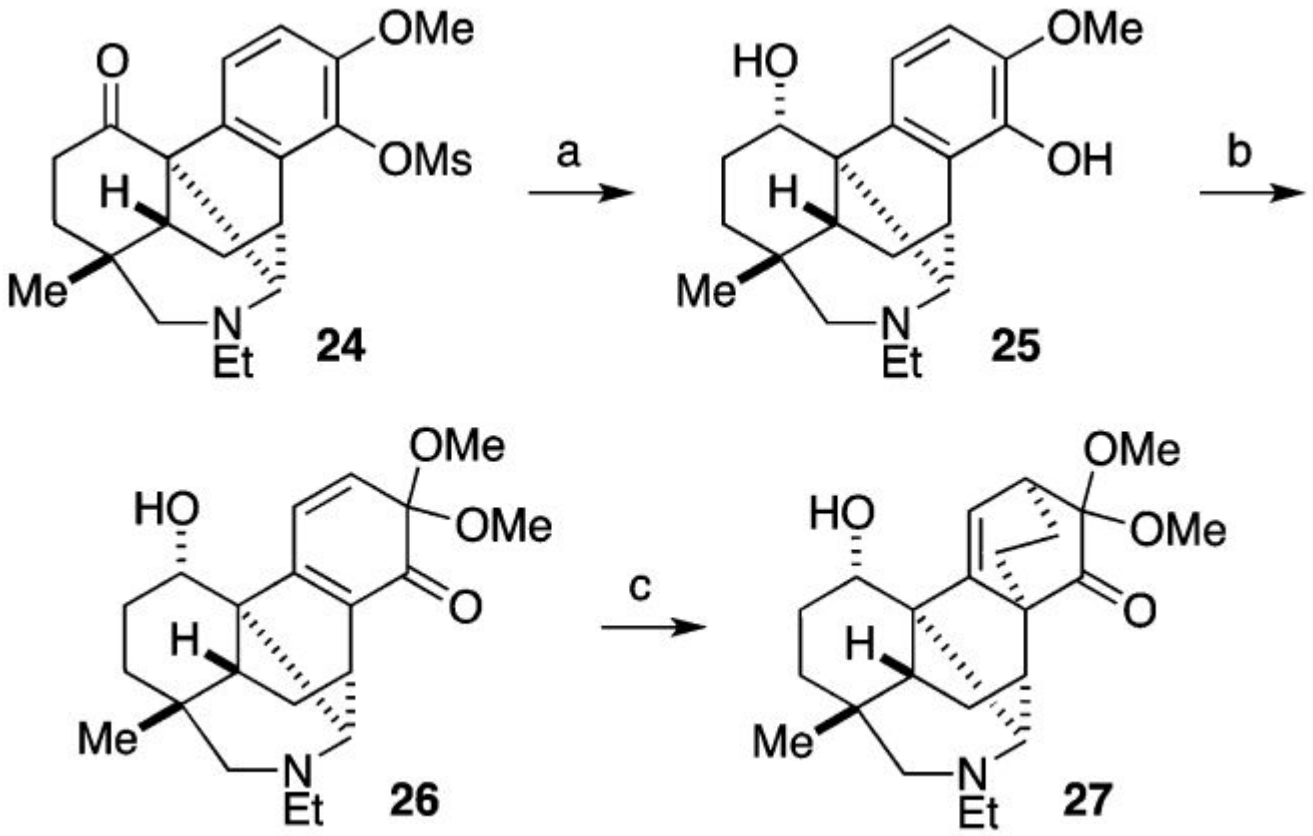
(a) guaiacol, Ph_3P, DEAD, toluene, 0 °C,87%, >99% ee;
(b) i-Bu_2AlH, Et_2O, hexane, −78 to −40 °C; vinylmagnesium chloride, THF, −40 to 0 °C, 94% (1:1.6 mixture);
(c) 4-$O_2NC_6H_4OH$ (5 mol %), $(EtO)_3CMe$, reflux, 9 d, 85%;
(d) MsCl, Et_3N, CH_2Cl_2, 0 °C, 85%;
(e) O_3, CH_2Cl_2, MeOH, −78 °C; $NaBH_4$, −78 to 0 °C, 86%;
(f) PivCl, pyridine, DMAP, CH_2Cl_2, rt, 80%, 91% ee;
(g) aq LiOH, THF, MeOH, 0 °C;
(h) TFAA, TFA, CH_2Cl_2, rt,
82% (two steps);
(i) vinylmagnesium chloride, THF, −40 °C, 85%;
(j) AgOTf (5 mol %), toluene (20 mM), reflux, 1 h,63%;
(k) i-Bu_2AlH,hexane, CH2Cl2, 0 °C, 89%;
(l) methacrylic acid, DCC, DMAP, CH2Cl2, rt, 85%;
(m) BHT, PhCN (20 mM), 160 °C, 6 h, 90%;
(n) crystallization from CHCl3/hexane (1:2), 84%.

Внутримолекулярная реакция Манниха



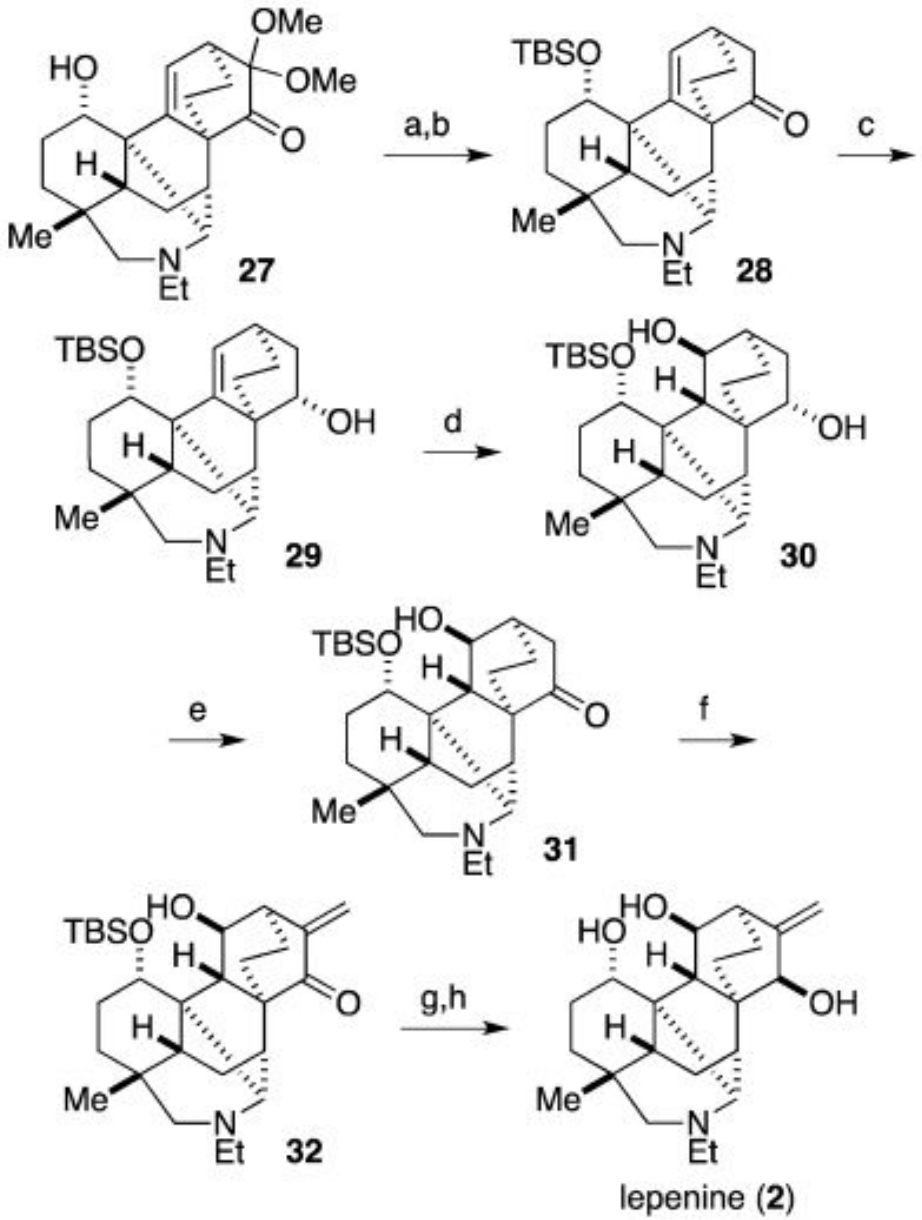
(a) BH3·THF, THF, rt; MeOH, 0 °C; aq NaOH, aq H2O2, 97%;
(b) i-Bu2AlH, hexane, CH2Cl2, −40 °C, 97%;
(c) EtNH2·HCl, Et3N, AcOH, MeCN, rt; NaBH(OAc)3; aq NaOH, 0°C; AllocCl, 93%;
(d) Dess−Martin periodinane, CH2Cl2, rt, 79%;
(e) Pd(PPh3)4, AcOH, CH2Cl2, reflux, 75%.

Построение бицикло [2,2,2]-скелета



(a) KOH, MeOH, 60 °C, 3 h; NaBH4, 0°C, 95%;
(b) methyl red, AcCl, MeOH, rt; PhI(OAc)2, 0 °C, 88%;
(c) ethylene (70 bar), CH2Cl2, 70 °C, 5 d, 84%.

Полный синтез лепенина (2)



(a) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt, 91%;
(b) SmI_2, MeOH, THF, 0 °C, 96%;
(c) Red-Al, toluene, 0 °C, 88%;
(d) $BH_3 \cdot THF$, THF, rt; H_2O, 0 °C; $NaBO_3 \cdot H_2O$, 0 °C to rt, 54%;
(e) Dess−Martin periodinane, TFA, CH_2Cl_2, rt, 72%;
(f) HCO_2Et, KHMDS, toluene, 70° C; aq HCHO, THF, 50 °C, 70%;
(g) $NaBH_4$,$CeCl_3 \cdot 7H_2O$, MeOH, 0 °C, 83%;
(h) TBAF, THF, 65 °C, 93%.