

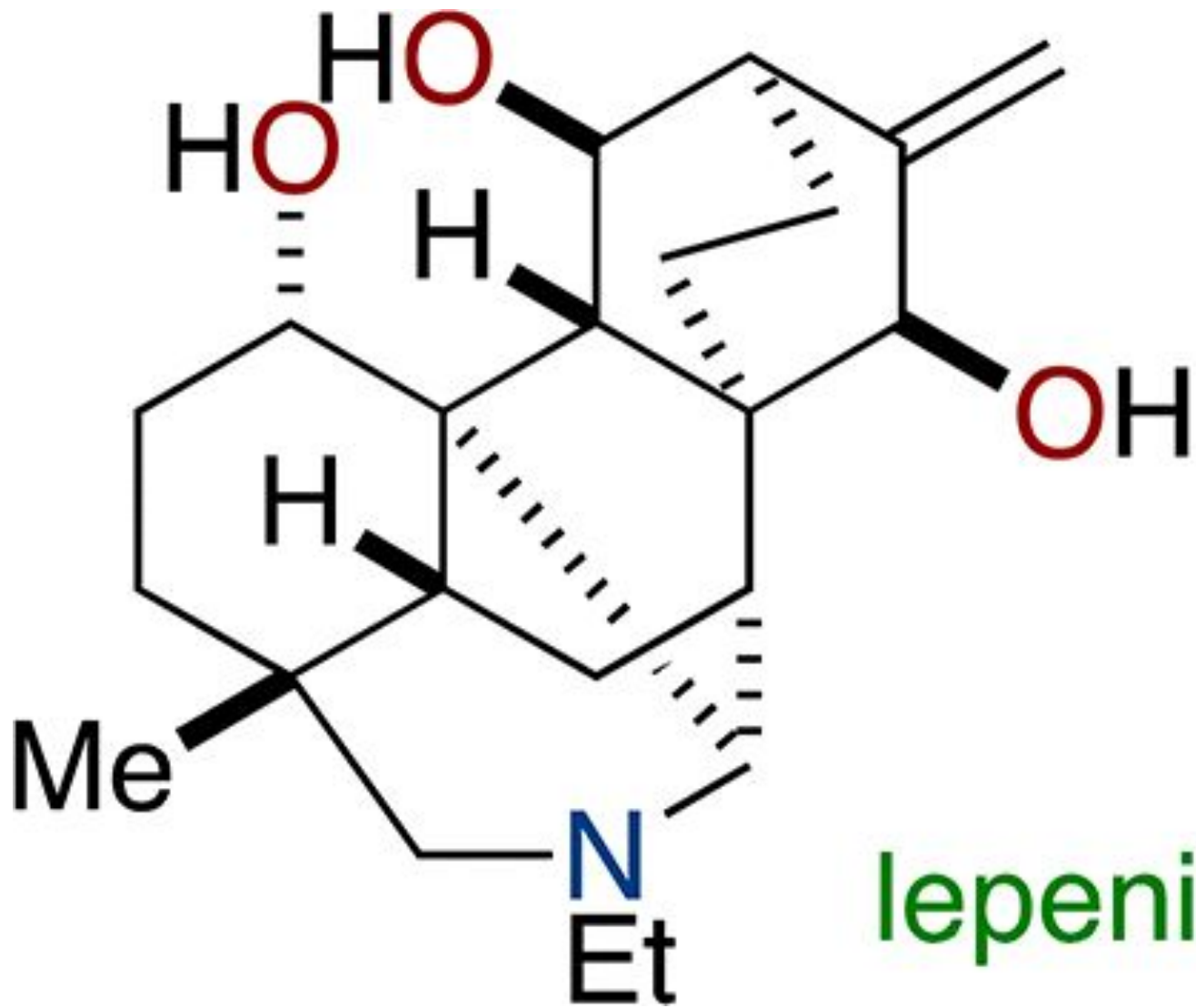


Total Synthesis of (-)-Lepenine

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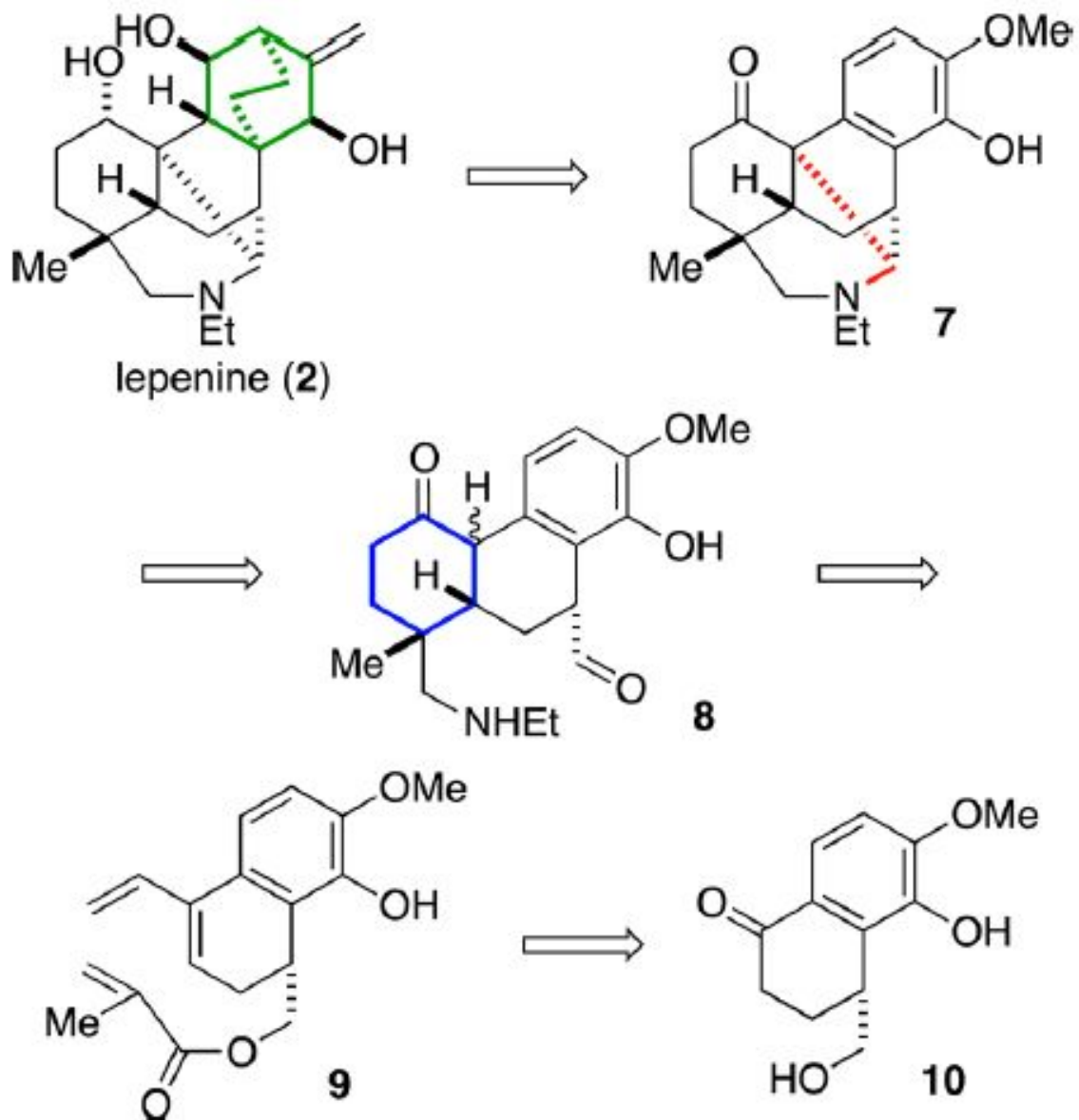
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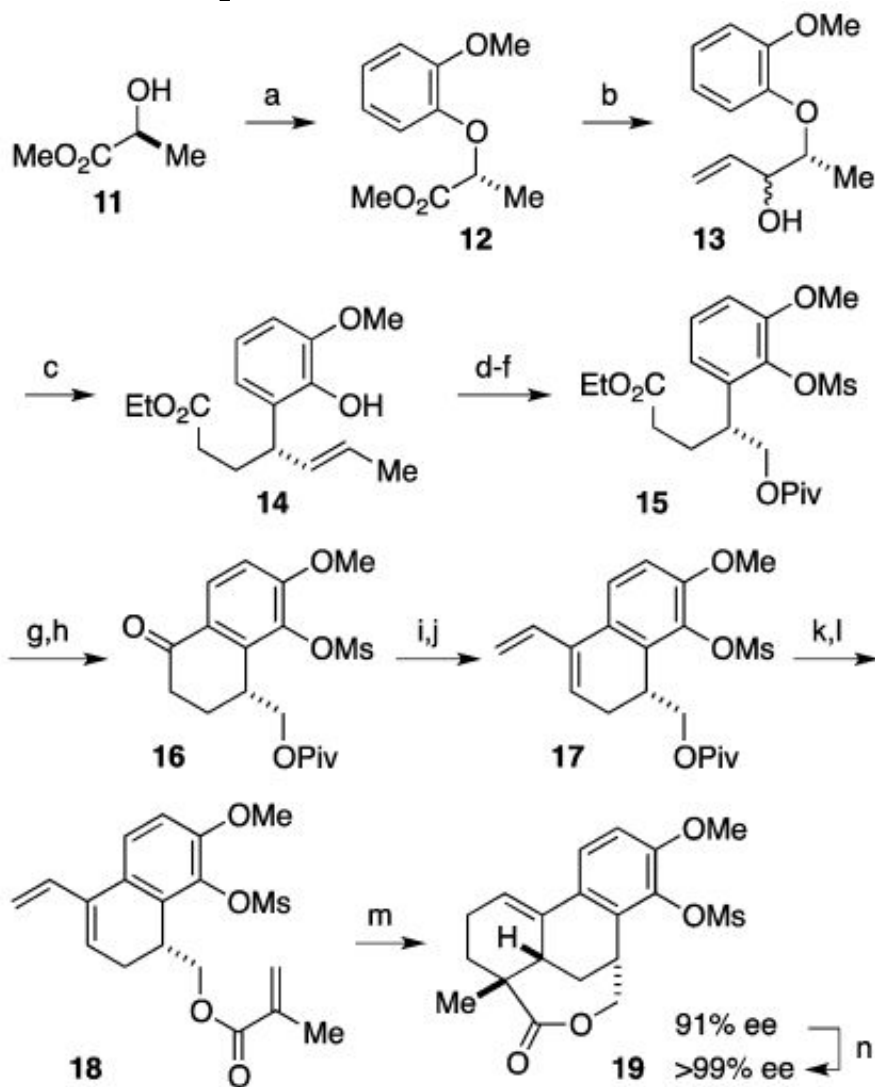


lepenine

Ретросинтетическая схема



Синтез фенантренового каркаса



(a) guaiacol, Ph_3P , DEAD, toluene, 0°C , 87%, >99% ee;

(b) $i\text{-Bu}_2\text{AlH}$, Et_2O , hexane, -78 to -40°C ; vinylmagnesium chloride, THF, -40 to 0°C , 94% (1:1.6 mixture);

(c) $4\text{-O}_2\text{NC}_6\text{H}_4\text{OH}$ (5 mol %), $(\text{EtO})_3\text{CMe}$, 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%;

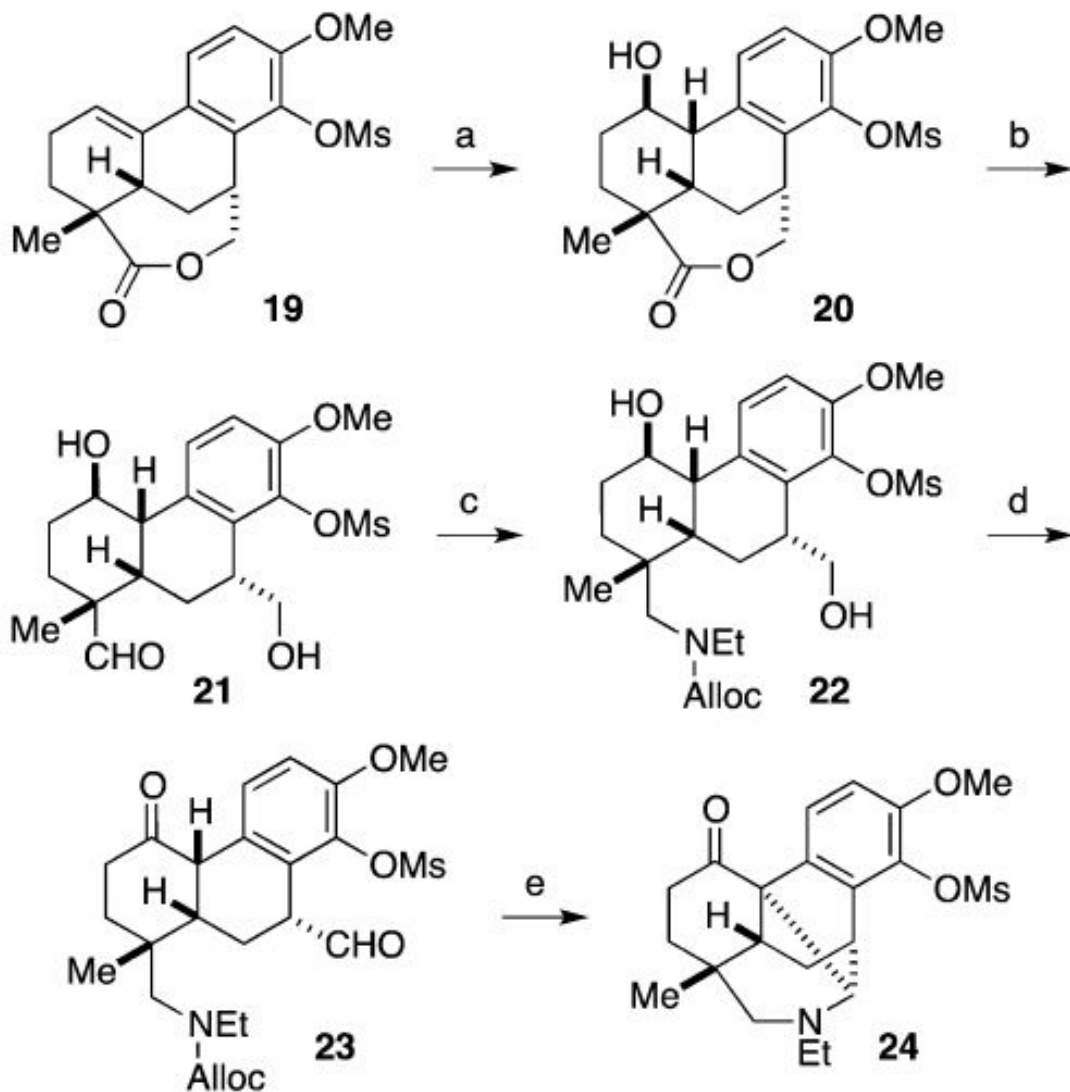
(k) $i\text{-Bu}_2\text{AlH}$, hexane, CH_2Cl_2 , 0°C , 89%;

(l) methacrylic acid, DCC, DMAP, CH_2Cl_2 , rt, 85%;

(m) BHT, PhCN (20 mM), 160°C , 6 h, 90%;

(n) crystallization from $\text{CHCl}_3/\text{hexane}$ (1:2), 84%.

Внутримолекулярная реакция Манниха



(a) $\text{BH}_3 \cdot \text{THF}$, THF, rt; MeOH, 0°C ; aq NaOH, aq H_2O_2 , 97%;

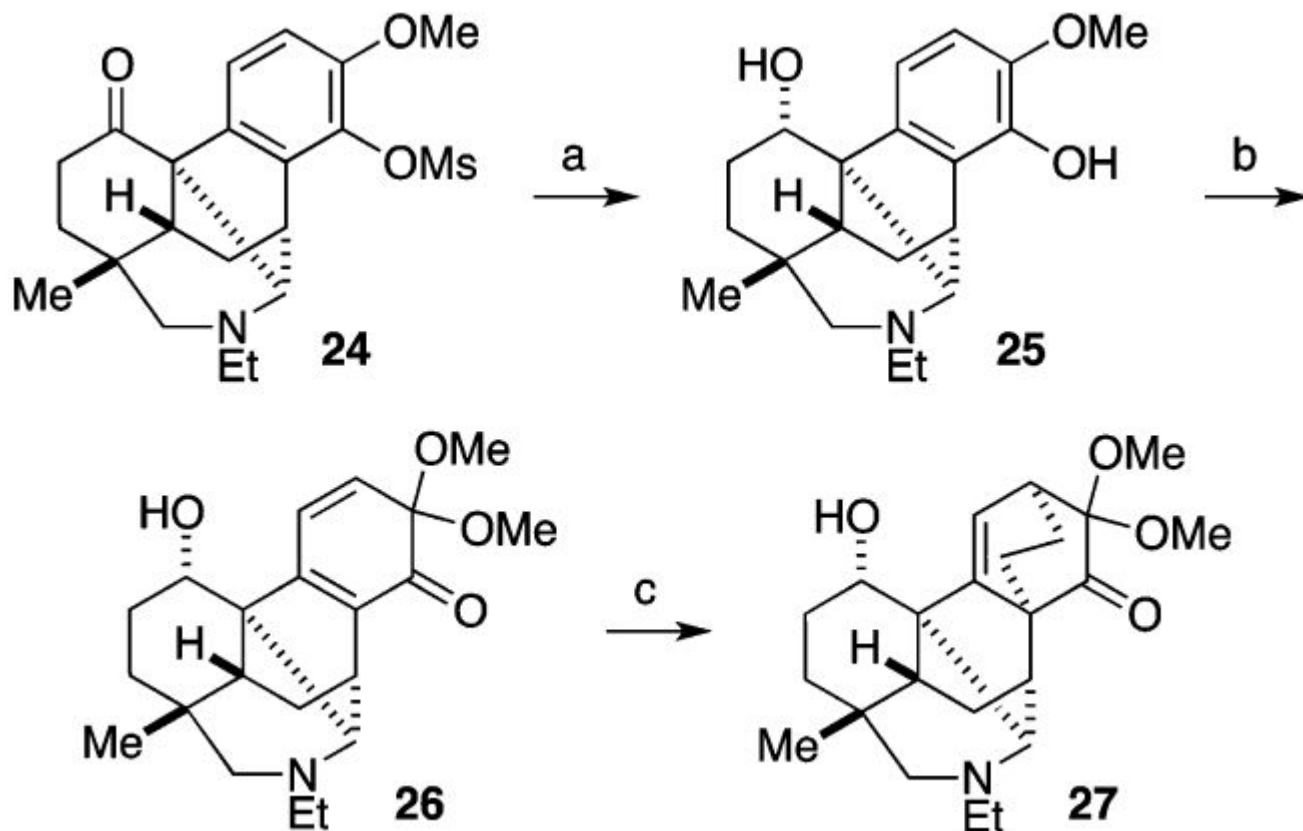
(b) $i\text{-Bu}_2\text{AlH}$, hexane, CH_2Cl_2 , -40°C , 97%;

(c) $\text{EtNH}_2 \cdot \text{HCl}$, Et_3N , AcOH, MeCN, rt; $\text{NaBH}(\text{OAc})_3$; aq NaOH, 0°C ; AllocCl, 93%;

(d) Dess–Martin periodinane, CH_2Cl_2 , rt, 79%;

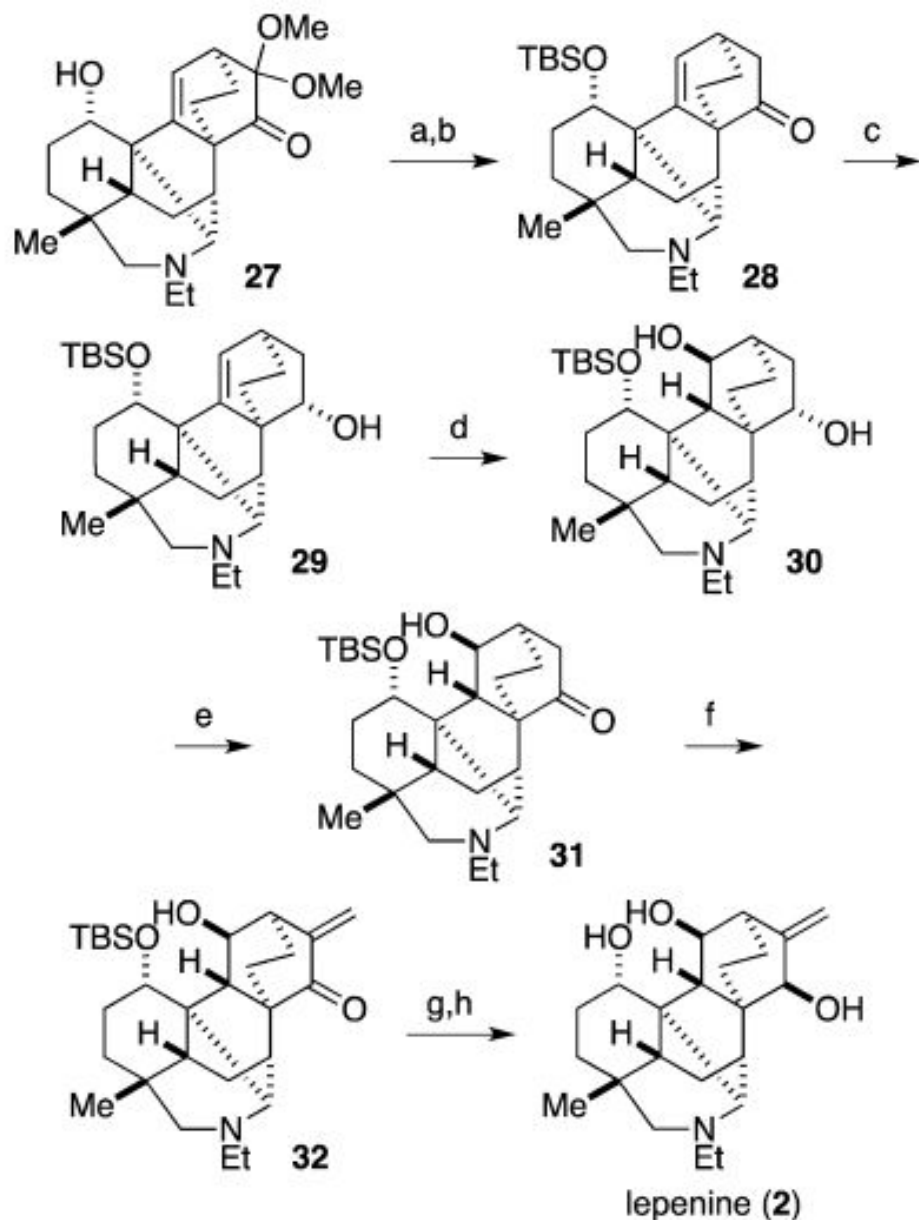
(e) $\text{Pd}(\text{PPh}_3)_4$, AcOH, CH_2Cl_2 , reflux, 75%.

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, CH₂Cl₂, rt, 91%;

(b) SmI₂, MeOH, THF, 0 °C, 96%;

(c) Red-Al, toluene, 0 °C, 88%;

(d) BH₃·THF, THF, rt; H₂O, 0 °C; NaBO₃·H₂O, 0 °C to rt, 54%;

(e) Dess–Martin periodinane, TFA, CH₂Cl₂, rt, 72%;

(f) HCO₂Et, KHMDS, toluene, 70 °C; aq HCHO, THF, 50 °C, 70%;

(g) NaBH₄, CeCl₃·7H₂O, MeOH, 0 °C, 83%;

(h) TBAF, THF, 65 °C, 93%.