Angewandte
Communications

Total Synthesis of (+)–Rubriflordilactone A

Так же известный как

(3aR,5aS,9aR,10S,11S,14aR)–5,5,10–trimethyl–11–((S)–4–methyl–5–oxo–2,5–dihydrofuran–2–yl)–3,3a,5,5a,6,7,8,9,9a,10,11,14–dodecahydro–2H–cyclopenta[de]furo[3'',2'':2',3']furo[3',4':4,5]cyclohepta[1,2–g]chromen–2–one

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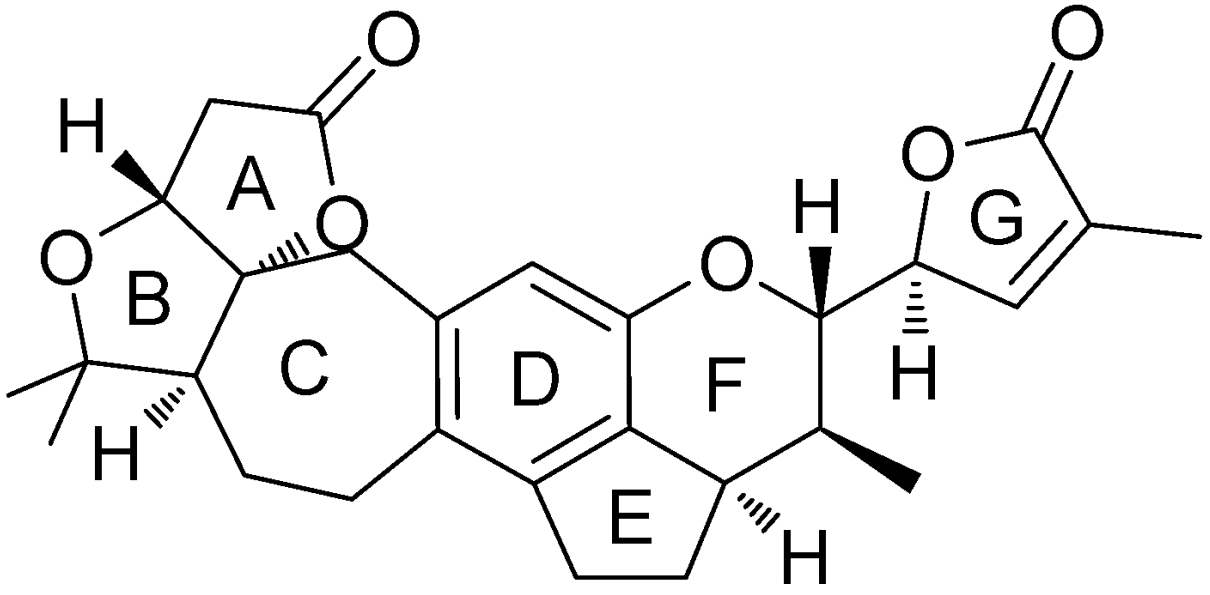
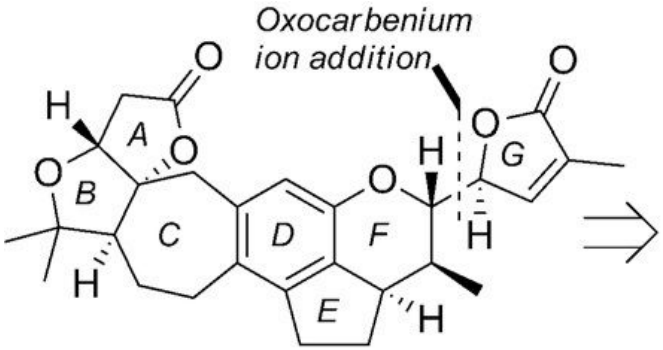
Natural Product Synthesis

(+)–Rubriflordilactone A



Стратегия синтеза, два пути



1: *Rubriflordilactone A*

Ключевые прекурсоры

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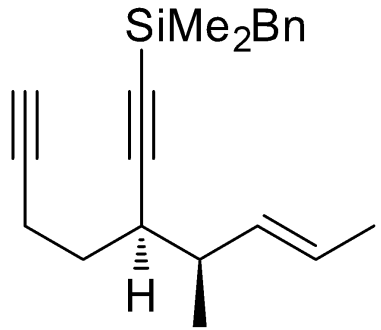
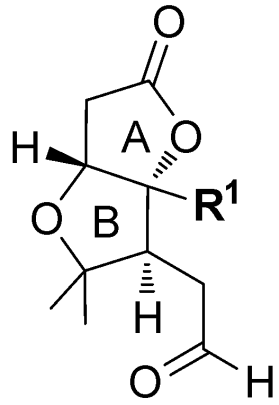


7

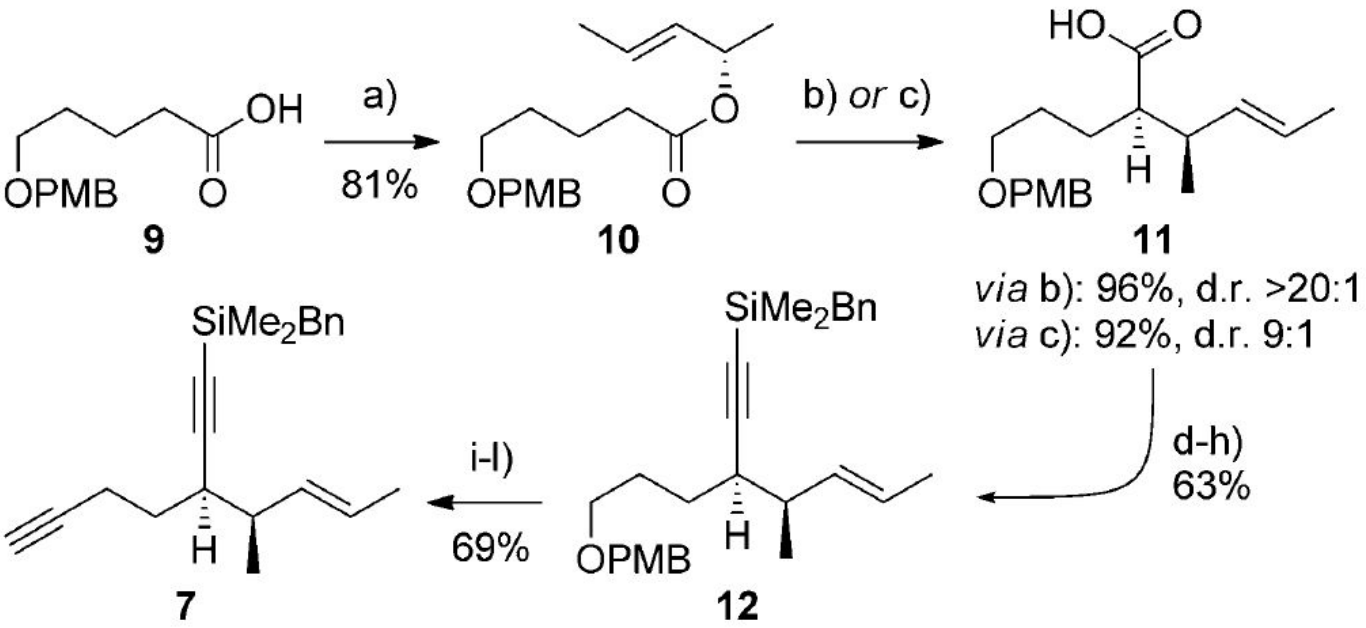
“ДИИН”



6: $R^1 = CH_2CBr{=}CH_2$

8: $R^1 = CH_2C{\equiv}CH$

Синтез диина **7**

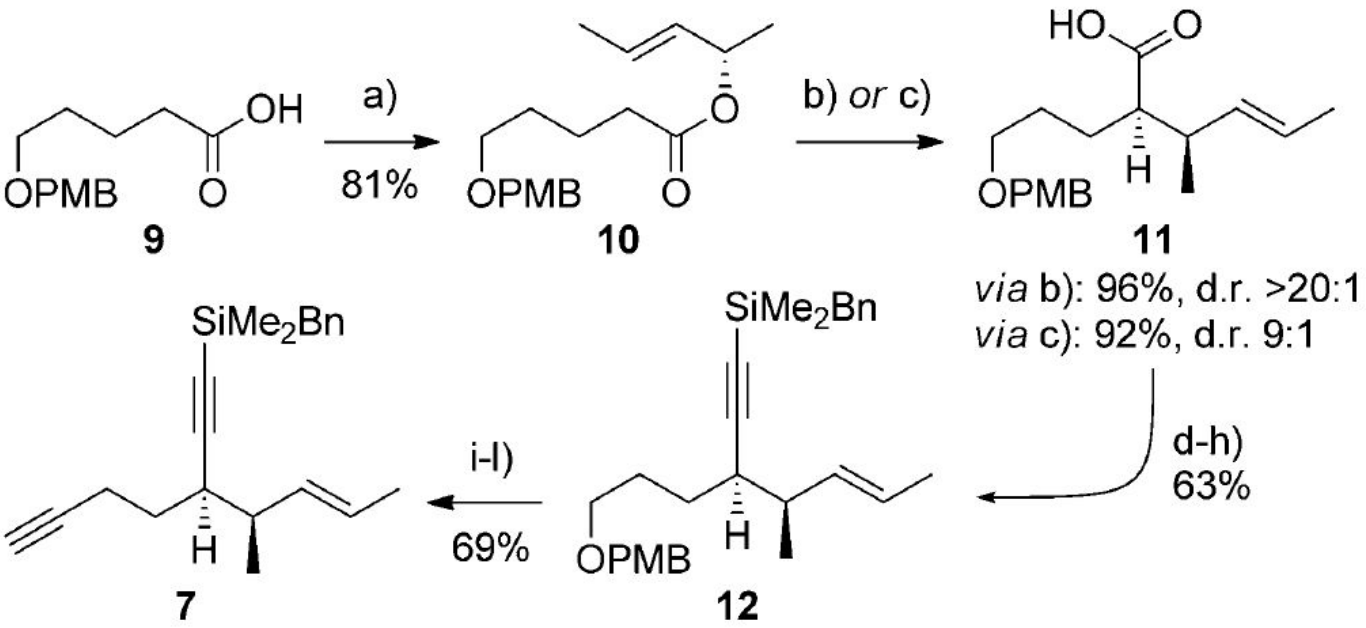


a) (S,E)-pent-3-en-2-ol, **EDC·HCl**, Et_3N, DMAP, THF, RT, 16 h, 81 %
b) LiHMDS, Et_3N/toluene (3:1), –78 c.d. □ RT, 5 h, 95%, d.r.>20:1
c) LDA, TMSCl/Et_3N (1:1), THF, –78 c.d. □ 0 c.d., 3 h, 92%, d.r. 9:1
d) TMSCHN2, toluene/MeOH (5:1), RT, 30 min, 88%
e) DIBALH, CH2Cl2, –78 cd □ 30 cd, 2 h, 97%
f) DMP, NaHCO3, CH2Cl2, 0 cd □ RT, 1 h, 90%
g) $[Ph_3PCH_2I]^+I^-$, NaHMDS, THF,–78 cd □ RT; then NaHMDS, –78 cd □ RT, 84%
h) LiHMDS, THF, –78 cd, 30 min; then $BnMe_2SiCl$, –78 cd □ RT, 3 h, 98%

b, c) - Ireland-Claisen rearr.

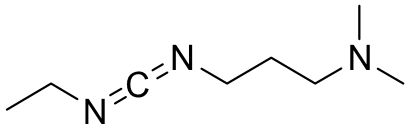
g) Stork-Zhao olefination

Синтез диина **7**



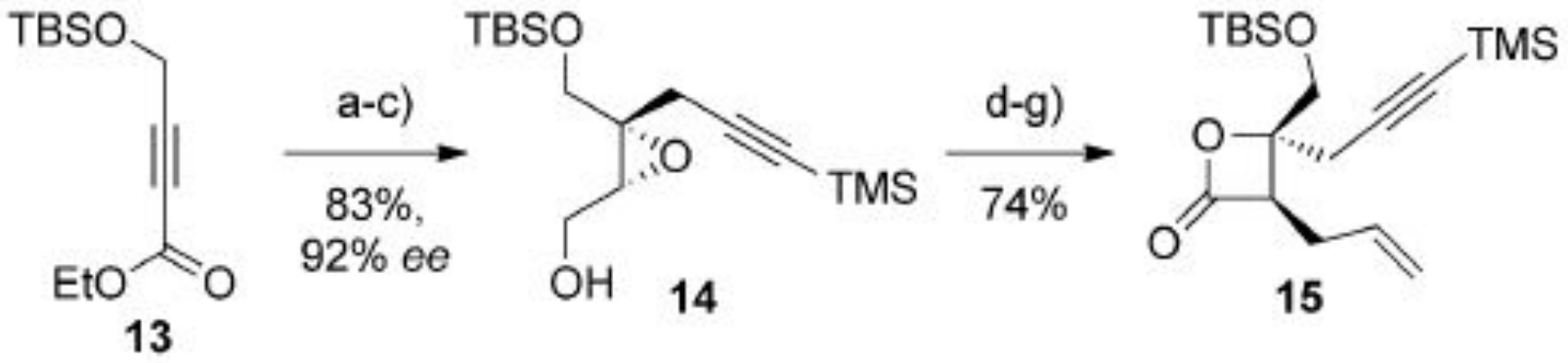
i) DDQ, CH2Cl2/H2O (4:1), RT, 1 h;
j) DMP, NaHCO3, CH2Cl2, 0 cd □RT, 30 min, 83% (2 steps);
k) CBr4, PPh3, CH2Cl2 –30 cd□ 0 cd, 1 h, 85%;
l) *n*BuLi, THF, –78 cd □RT, 40 min, 98%.

EDC = 1–Ethyl–3–(3–dimethylaminopropyl)carbodiimide



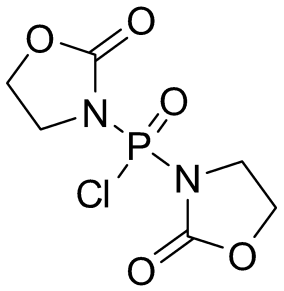
DMP = Dess–Martin Periodinane

Синтез альдегида **8**, начало

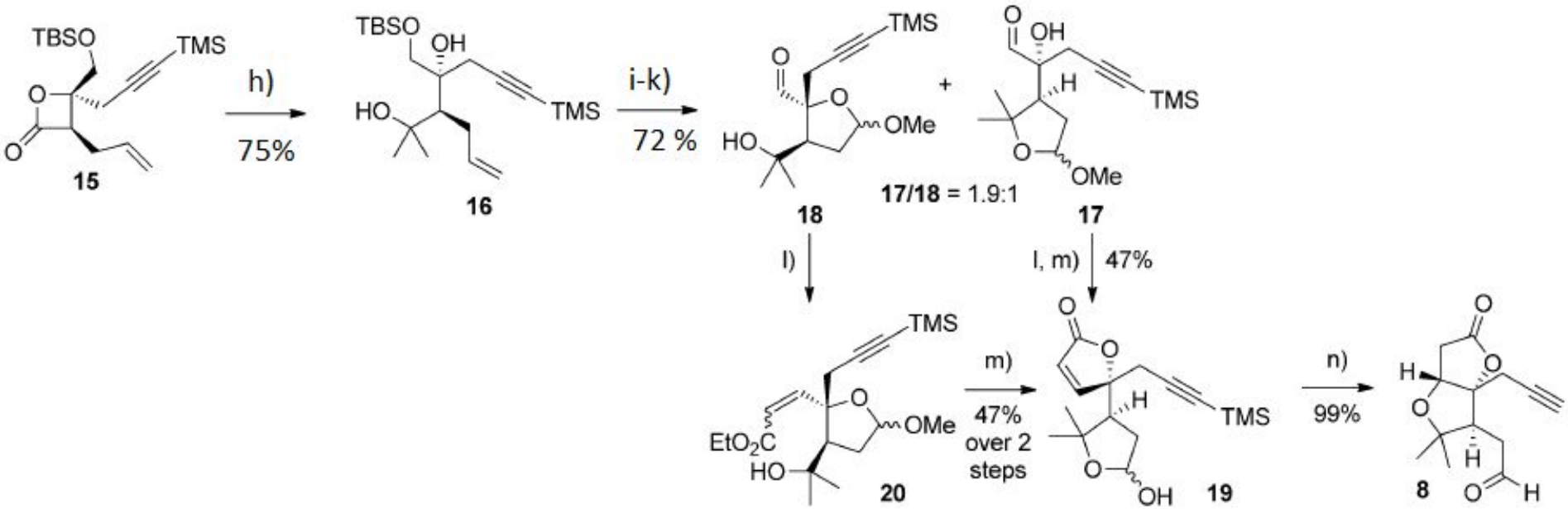


a) TMSC≡CCH2MgBr, CuBr·SMe2, THF, –78cd □ –40 cd, 40 min; **13**, –78 cd
b) DIBALH, CH2Cl2, –78 cd □ RT, 3 h, 90% (2 steps)
c) $Ti(OiPr)_4$, D-(—)-diethyl tartrate, tBuOOH, 4 **Å** MS, CH2Cl2, –20 cd, 22 h, 92%, 92% ee
d) AllylMgBr, THF, 08C, 10 min, 97%
e) SO3·py, DMSO, iPr2EtN, CH2Cl2, 0 cd □ RT, 2 h
f) NaOCl, NaH2PO4, 2–methylbut–2–ene, tBuOH/H2O (3:1), RT, 18 h, 92% (2 steps)
g) BOPCl, py, MeCN, RT, 3 h, 83%

BOPCl = bis(2-oxo–3-xazolidinyl)-phosphinic chloride

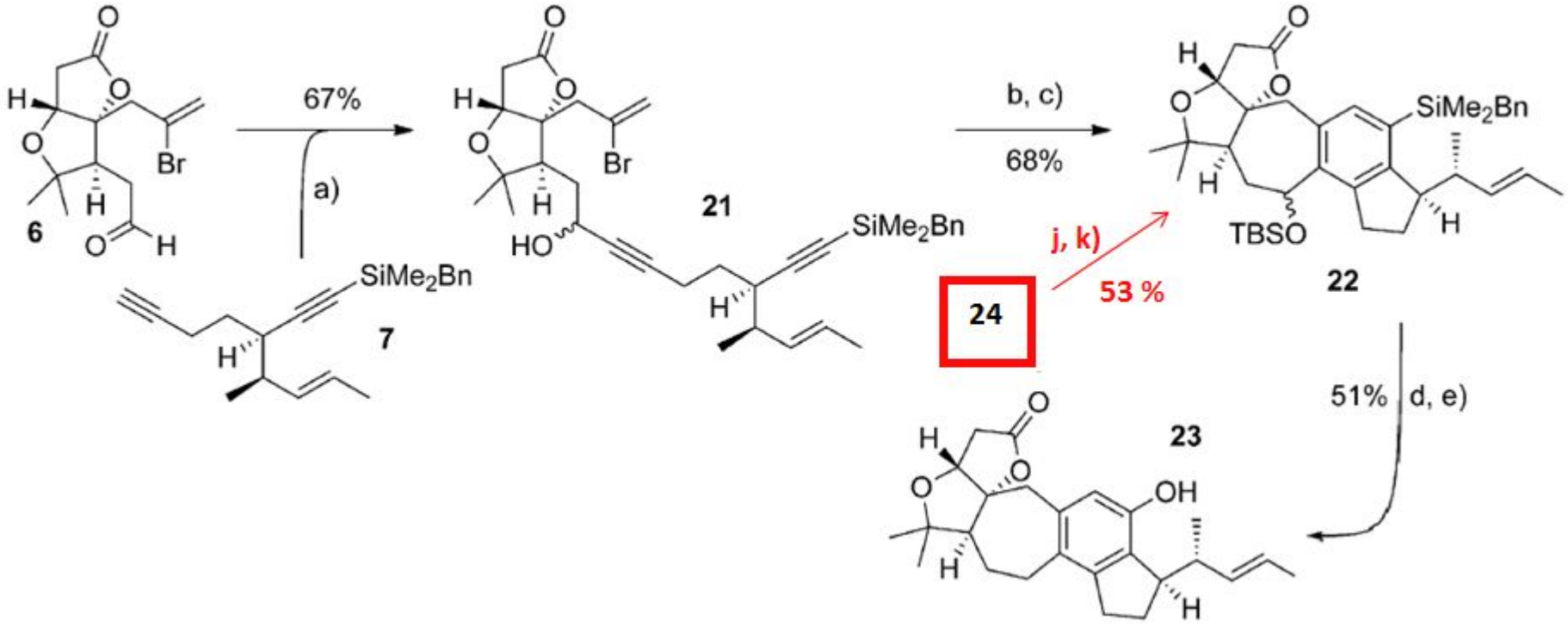


Синтез альдегида **8**, конец



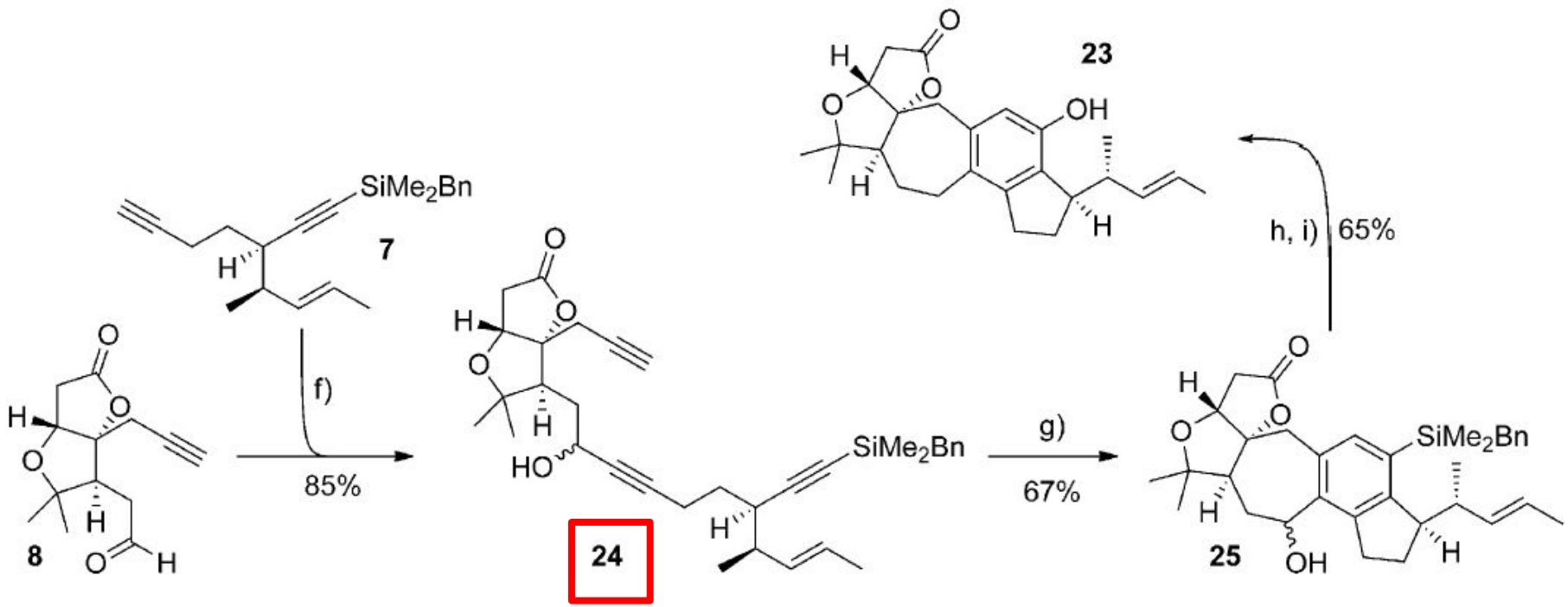
h) MeMgBr, THF, –58 cd □ RT, 1.5 h, 64%+31% ketone, recycled to give 75% overall
i) OsO4, NaIO4, 2,6–lutidine, dioxane/H2O (4.6:1), RT, 2 h, 88%
j) (±□)–camphorsulfonic acid, MeOH, RT, 18 h, 98%
k) SO3·py, DMSO, iPr2EtN, CH2Cl2, 0–10 cd, 1 h, 84%
l) (PhO)2POCH2CO2Et, KHMDS, THF, 0 cd
m) TFA, CH2Cl2, 08C, 15 min, 47% (from **17**, and **18**)
n) K2CO3, MeOH, RT, 2 h, 99%

Объединение прекурсоров (1)



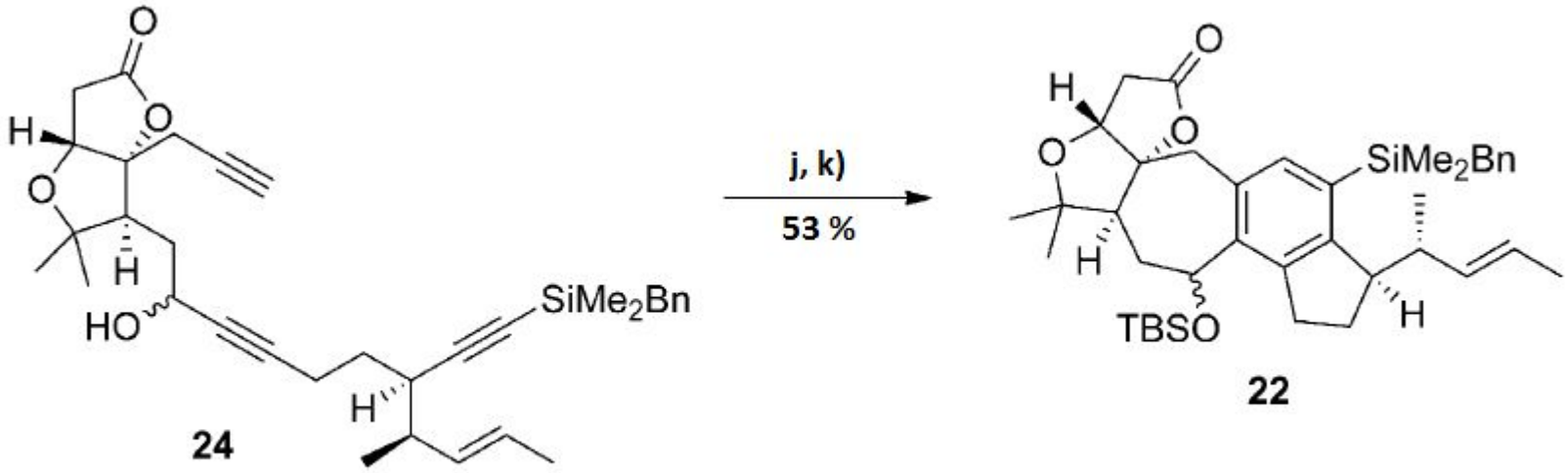
a) nBuLi, 7, –78 cd; then add **6**, –78 cd □ –10 cd, 2 h, 67%
b) TBSOTf, 2,6–lutidine, CH2Cl2, 0 cd □ RT, 4 h, 75%
c) [Pd(PPh3)4] (10 mol%), Et3N, MeCN, 80 cd, 18 h, 91%
d) TBAF, THF, RT, 30 min; then H2O2, KHCO3, MeOH, RT, 12 h
e) Et3SiH, ZnCl2, CH2Cl2, RT, 3 h; then TBAF, THF, RT, 20 min, 51% (2 steps)

Объединение прекурсоров (2)



f) nBuLi, 7, –78 cd; then add 8, –78 cd –10 cd, 4 h, 85%
g) [CpCo(CO)2] (20 mol%), PPh3 (40 mol%), PhCl, MW (300 W), 150 cd, 25 min, 67%
h) TBAF, THF, RT, 30 min; then H2O2, KHCO3, MeOH, RT, 12 h, 84%;
i) Et3SiH, ZnCl2, CH2Cl2, RT, 3 h, 77%;

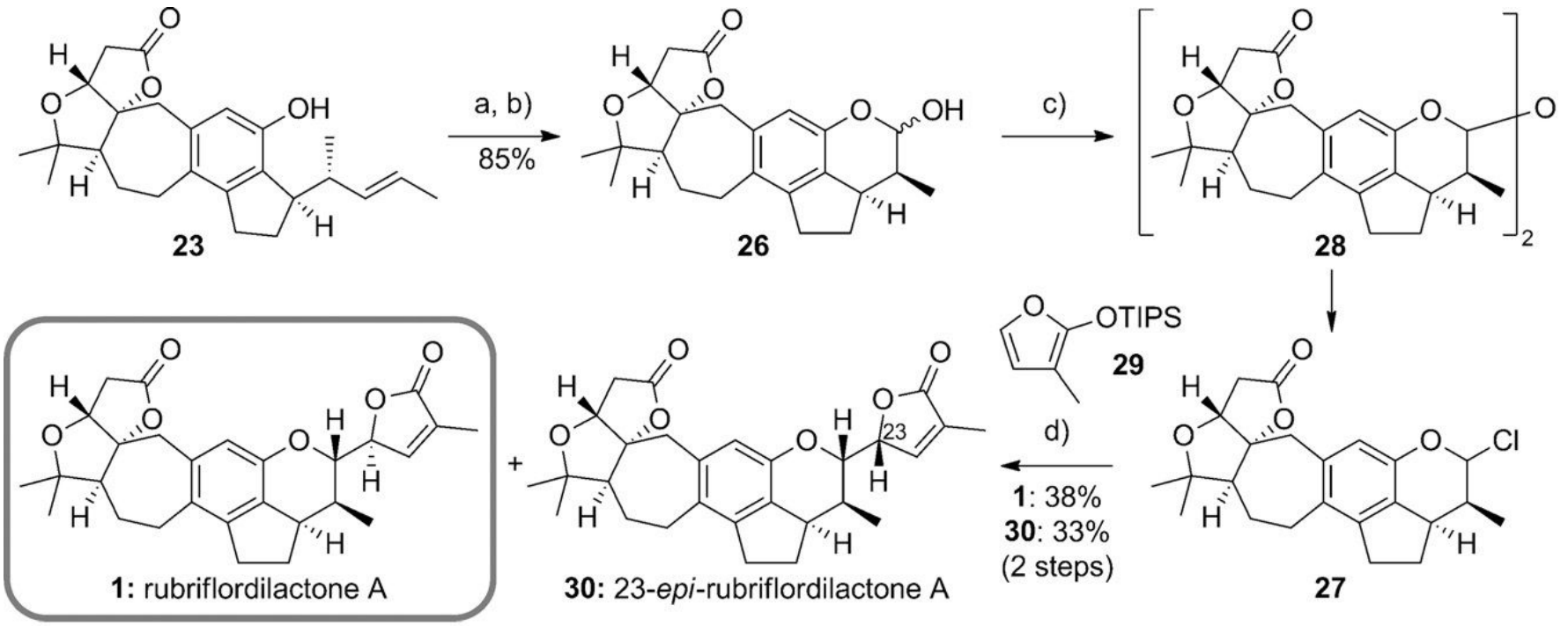
Переход от 24 к 22



j) TBSCl, imid., DMAP, CH2Cl2, RT, 6 h, 98%

k) [CpCo(CO)2] (20 mol%), PPh3 (40 mol%), PhCl, MW (300 W), 1508C, 25 min, 54%

Завершение синтеза



a) OsO4 (2 mol%), NMO, acetone/H2O (3:1), RT, 3 h

b) NaIO4/SiO2, CH2Cl2, RT, 15 min, 85% (2 steps)

c) ZnCl2, SOCl2, CDCl3, RT, 3 h

d) **29**, ZnCl2, CH2Cl2, ў308C!RT, 12 h, 38% of 1 and 33% of 30 (2 steps)

Спасибо за внимание