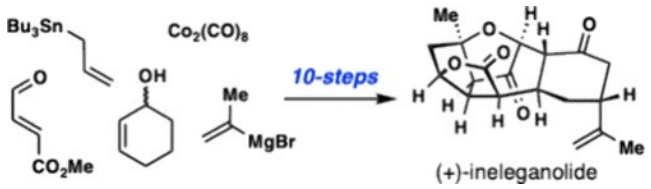
Short, Enantioselective Total Synthesis of (+)-Ineleganolide

Kuan Yu*, Aikaterini Gorou, Danny Huang, and Thomas J. Maimone*

Journal of the American Chemical Society 2025, 147, 49, 44727-44732

10-step asymmetric total synthesis

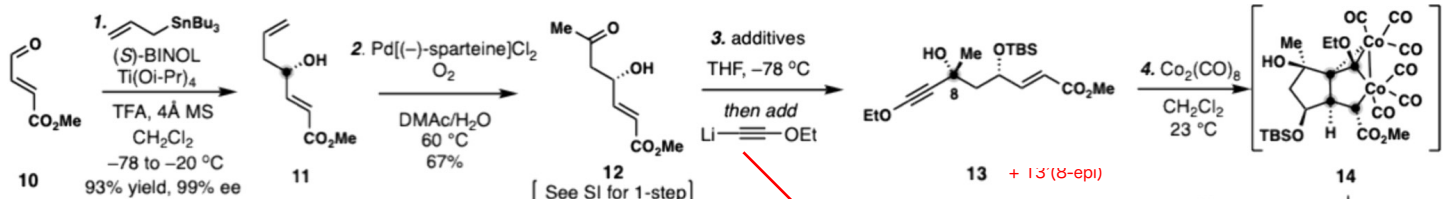
new abiotic blueprint



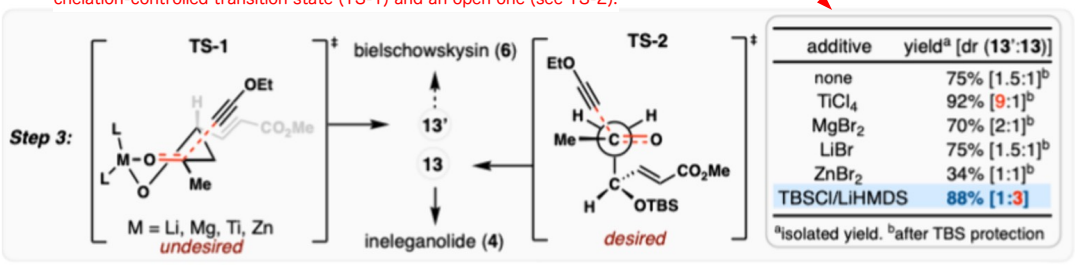
asymmetric Keck allylation

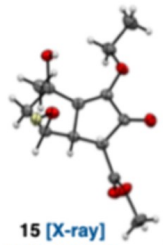
Sigman's modification:
traditional Tsuji-Wacker low yield

intramolecular Pauson–Khand (PK) reaction



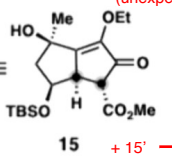
chelation-controlled transition state (TS-1) and an open one (see TS-2).





15 [X-ray]
(TBS omitted for clarity)

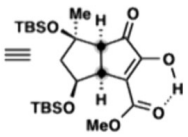
84% yield | dr = 13:1
endo addition (unexpected)



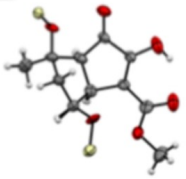
15 + 15'

5. TBSOTf
2,6-lutidine
23 °C
carefully

then add
HCl/HF·Py
55%



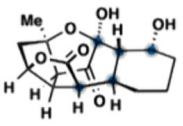
8



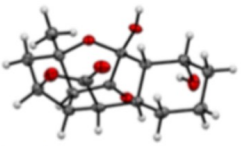
8 [X-ray]
(TBS omitted for clarity)

6. hv (300 nm)
MeCN
–20 °C
then add
1M HCl
52%
dr > 20:1

(±)
(2.5 equiv)
racemic

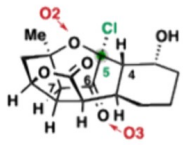


16



16 [X-ray]

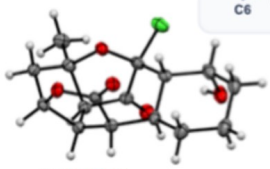
7. SO2Cl2
Et3N, DMAP
CH2Cl2
0 °C
79%



17

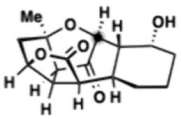
Newman Projection
θ = 161.4°

Overreduction of the β-keto



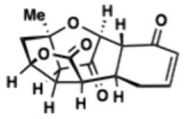
17 [X-ray]

8. SmI2
MeOH
THF, 0 °C
93%



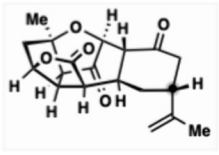
18

9. (PhSeO)2O
pyridine
PhMe, 90 °C
81%

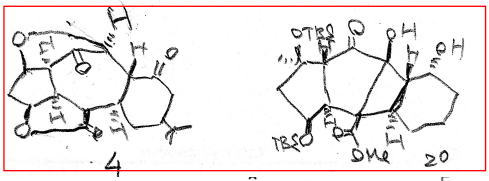


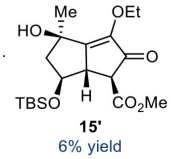
19

10. MeMgBr
CuBr·Me2S
THF, –78 °C
76% (85% brsm)
dr > 20:1
unexceptef



(+)-ineleganolide (4)

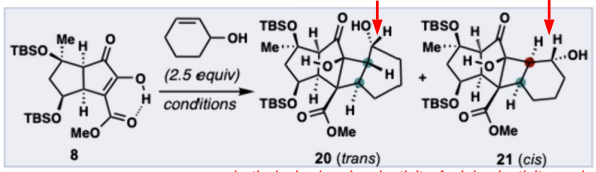




15'
6% yield

Table 1. Optimization of the Photochemical *trans*-[2 + 2] Cycloaddition[a,b,c,d,e,f]

single configuration



both desired regioselectivity, facial selectivity, and exo selectivity

Entry	Conditions	Yields (%)[b] 20	21
1[c]	Ir[dF(CF3)ppy]2(dtbbpy)PF6, Sc(OTf)3, terpy, imidazole 427 nm, CH2Cl2, 0.05 M, 23 °C, 15 h	0	0
2[c]	ZrCl4, 440 nm, CH2Cl2, 0.1 M, 23 °C, 14 h	0	0
3[c]	4CzIPN, n-Bu2PO4NMe(n-Bu)3, 455 nm, CH3CN, 0.1 M, 23 °C, 24 h	0	0
4[d]	Hg (450 W), benzene, 0.02 M or 0.1 M, 40 °C, 5 h	<10	<10
5[c]	390 nm, benzene, 0.02 M, 45 °C, 24 h	0	0
6	350 nm, benzene, 0.02 M, 45 °C, 16 h	25	25
7[e]	350 nm, CH2Cl2, 0.02 M, 0 °C, 15 h	<5	<5
8	300 nm, CH2Cl2, 0.02 M, –78 °C, 18 h	43	29
9[e]	254 nm, CH2Cl2, 0.02 M, –78 °C, 24 h	<5	<5
10[d]	300 nm, Et2O or EtOAc or acetone, 0.02 M, –78 °C, 16-24 h	<5	<5
11	300 nm, MeCN, 0.02 M, –20 °C, 9 h (20 h)[f]	67 (56)[f]	0
12[c]	300 nm, MeOH, 0.02 M, –78 °C, 24 h	0	0