

Total synthesis of (\pm)-Limonin

Yamashita, S. and co-workers

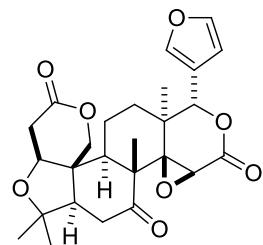
ACIE 2015, 54, 8538 (Hot paper)

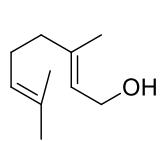
Flagship congener of Limonoids (triterpenoids from citrus fruits) - bitter component

First isolated in 1841

Structure first determined by Arigoni, Barton, Corey Jeger, and Robertson groups in 1960.

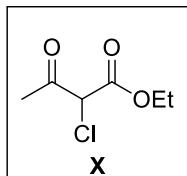
First total synthesis in 2015.





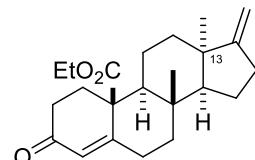
Name??

- a) PCl_3 , DMF, THF, rt
- b) mCPBA, K_2CO_3 , DCM, -60 to 20 °C
- c) $\text{TMS}-\text{CH}_2\text{Li}$
- d) $\text{Al}(\text{O}i\text{Pr})_3$, toluene, 110 °C
- e) SOCl_2 , Et_2O pentane, rt
- f) NaH , $n\text{BuLi} + \text{X}$
DMPU, THF, 0 °C

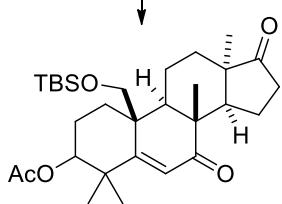


- g) TBAF
dr 2.1 : 1 for C13
- h) $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$, EtOH, rt
- i) Zn, AcOH, rt
- j) MVK, cat. tBuOK, tBuOH, 35 °C

- k) MeI, tBuOK, tBuOH, 40 °C
- l) LAH
- m) TBSCl, NaH, THF, 0 to 20 °C
- n) Ac_2O , Py, DMAP, DCM, rt



- o) mCBPA, NaHCO_3 , DCM, -20 to -5 °C
- p) NaCN, DMSO, 120 °C
- q) Ac_2O (Hint: used to convert a by-product to the desired intermediate)
- r) TBHP, CuBr, DCM, rt



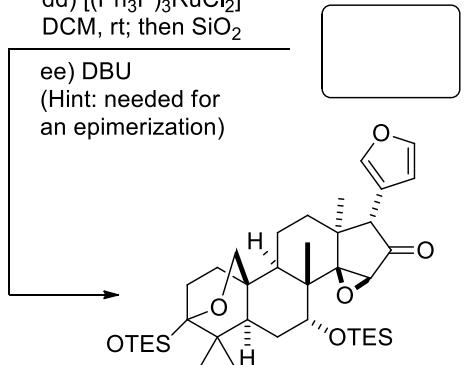
- s) Li, NH_3
- t) DMP, NaHCO_3 , DCM, rt
- u) TBAF
- v) $\text{LiAlH}(\text{OtBu})_3$, THF, -60 °C
- w) TESOTf, 2,6-lutidine, DCM, -40 to -20 °C

- x) Saegusa-Ito: conditions
- z) TfO_2 , DTBMP, DCM
- aa) Stille: Pd cat + what?

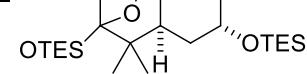


- dd) $[(\text{Ph}_3\text{P})_3\text{RuCl}_2]$
DCM, rt; then SiO_2

- ee) DBU
(Hint: needed for an epimerization)



- bb) O_2 , $\text{h}\nu$,
methylene blue
- cc) DIBAL-H, DCM, -90 °C
then AcO_2 , DMAP, -90 to 20 °C



- ff) $\text{H}_2\text{O}_2/\text{urea}$
aq. NaOH , MeOH, DME, 45 °C
- gg) TBAF

- hh) PIDA, I_2 , O_2 , $\text{h}\nu$
- ii) TPAP
- jj) TPAP, NMO

LIMONIN