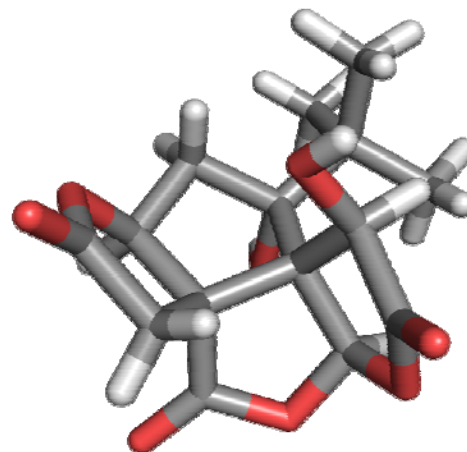
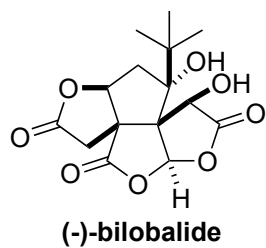


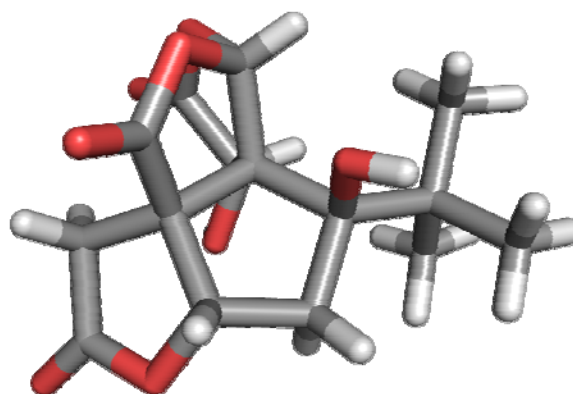
Problem Session (10)

2018/09/01 MASANORI NAGATOMO

Please propose your synthetic route to (-)-bilobalide from a commercially available compound.

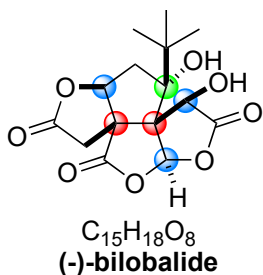


CCDC: 1160643

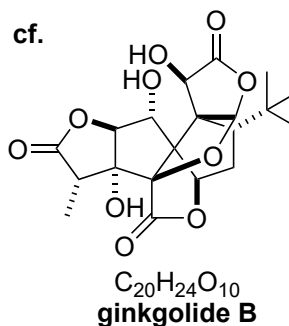


Problem Session (10)- Answer

Synthetic Plan of (-)-Bilobalide



2018/09/01 MASANORI NAGATOMO



Isolation: Sesquiterpenoid isolated from Ginkgo leaves

Major, R. T. *Science* **1967**, 157, 1270.

Nakanishi, K.; Habguchi, K.; Nakadaira, Y.; Woods, M.C.; Maruyama, M.; Major, R. T.; Alauddin, M.; Patel, A. R.; Weinges, K.; Bahr, W. *J. Am. Chem. Soc.* **1971**, 93, 3544.

Bioactivities: neuroprotective effects, negative allosteric modulator at the GABA_A and GABA_A-rho receptors

Structural features: Terpene trilactones (TTLs) having six contiguous stereocenters including two successive quaternary carbons and *t*-Bu group. A similar structure to ginkgolide families

Racemic total syntheses

Corey, E. J.; Su, W. G. *J. Am. Chem. Soc.* **1987**, 109, 7534. [22 steps]

Crimmins, M. T.; Jung, D. K.; Gray, J. L. *J. Am. Chem. Soc.* **1993**, 115, 3146. [18 steps]

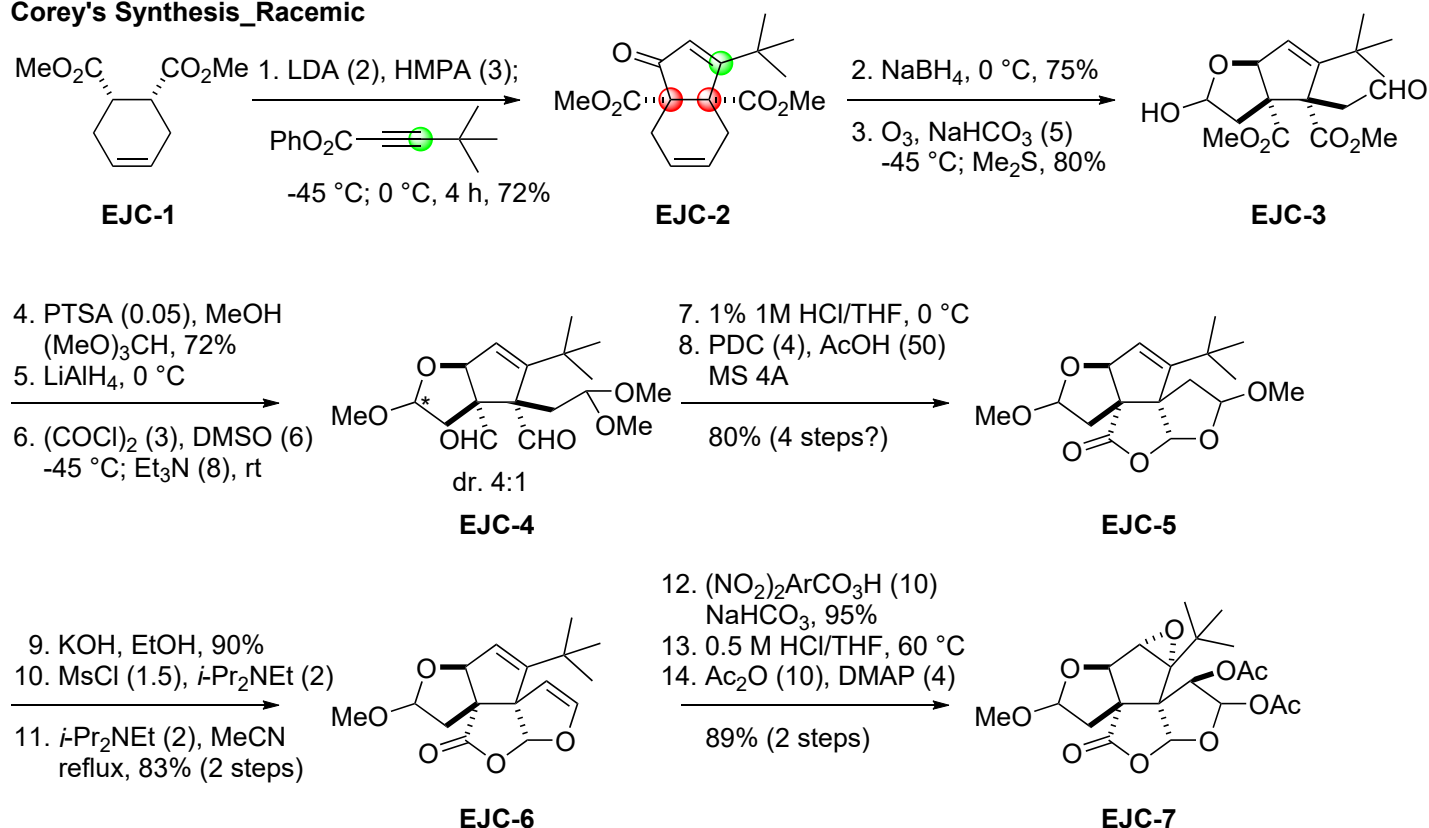
Asymmetric total synthesis

Corey, E. J.; Su, W. G. *Tetrahedron Lett.* **1988**, 29, 3423. [24 steps]

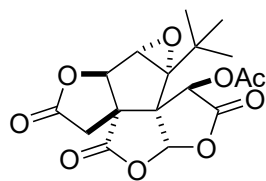
Recent synthetic study

Emsermann, J.; Opartz, T. *Eur. J. Org. Chem.* **2017**, 3362.

Corey's Synthesis_Racemic

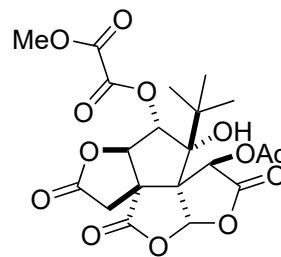


15. *m*-CPBA (7)
 BF₃·OEt₂ (3)
 60 °C, 92%
16. 0.5 M HCl/THF, 80 °C
 17. PDC (4) 96% (2 steps)



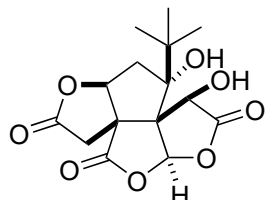
EJC-8

18. Et₃SiH, 300 °C, 90%
 19. OsO₄, py.
20. MeO₂CCOCl (1.3)
i-Pr₂NEt (2), 0 °C
 100% (2 steps?)



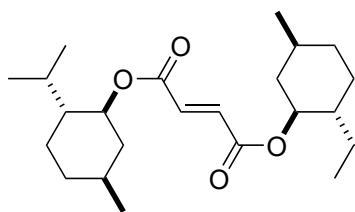
EJC-9

21. *n*-Bu₃SnH (3)
 AIBN (0.05)
 toluene, reflux
 55% (diol 30%)
22. 3 M HCl aq. reflux, 70%



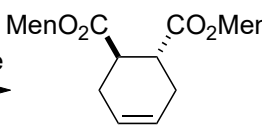
rac-bilobalide

Corey's Synthesis_Asymmetric



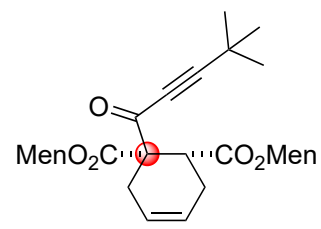
EJC-10

1. butadiene
i-Bu₂AlCl (2)
 CH₂Cl₂/hexane
 88%



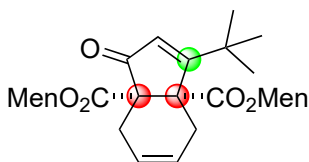
EJC-11

2. LDA (1), THF
 -78 °C, 2 h;
 PhO₂C-C≡C-C(CH₃)₃
- 91%



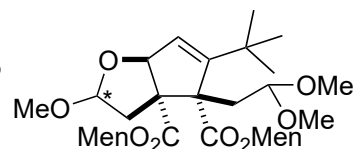
EJC-12

3. KN(TMS)₂ (0.5)
 -45 °C, 24 h
 80%



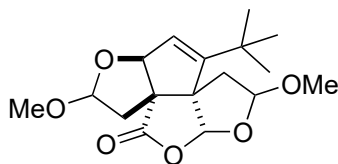
EJC-13

4. CBS-reduction, 41%
5. O₃, NaHCO₃ (5)
 -45 °C; Me₂S
6. PTSA (0.05), MeOH
 (MeO)₃CH, 60 °C
 75% (2 steps)



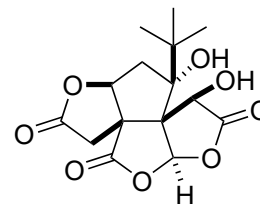
EJC-14

7. LiAlH₄, 55 °C, 84%
 8. (COCl)₂, DMSO, Et₃N
9. 1% 1M HCl/THF, 0 °C
 10. PDC, MS 4A
 62% (3 steps?)



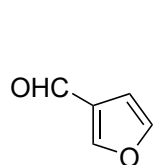
EJC-15

the same 14 steps



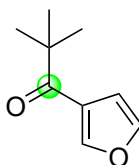
(-)-bilobalide

Crimmins' Synthesis_Racemic



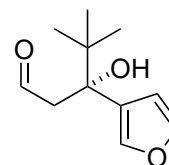
MTC-1

1. *t*-BuLi, CeCl₃, -78 °C
 2. (COCl)₂, DMSO, Et₃N



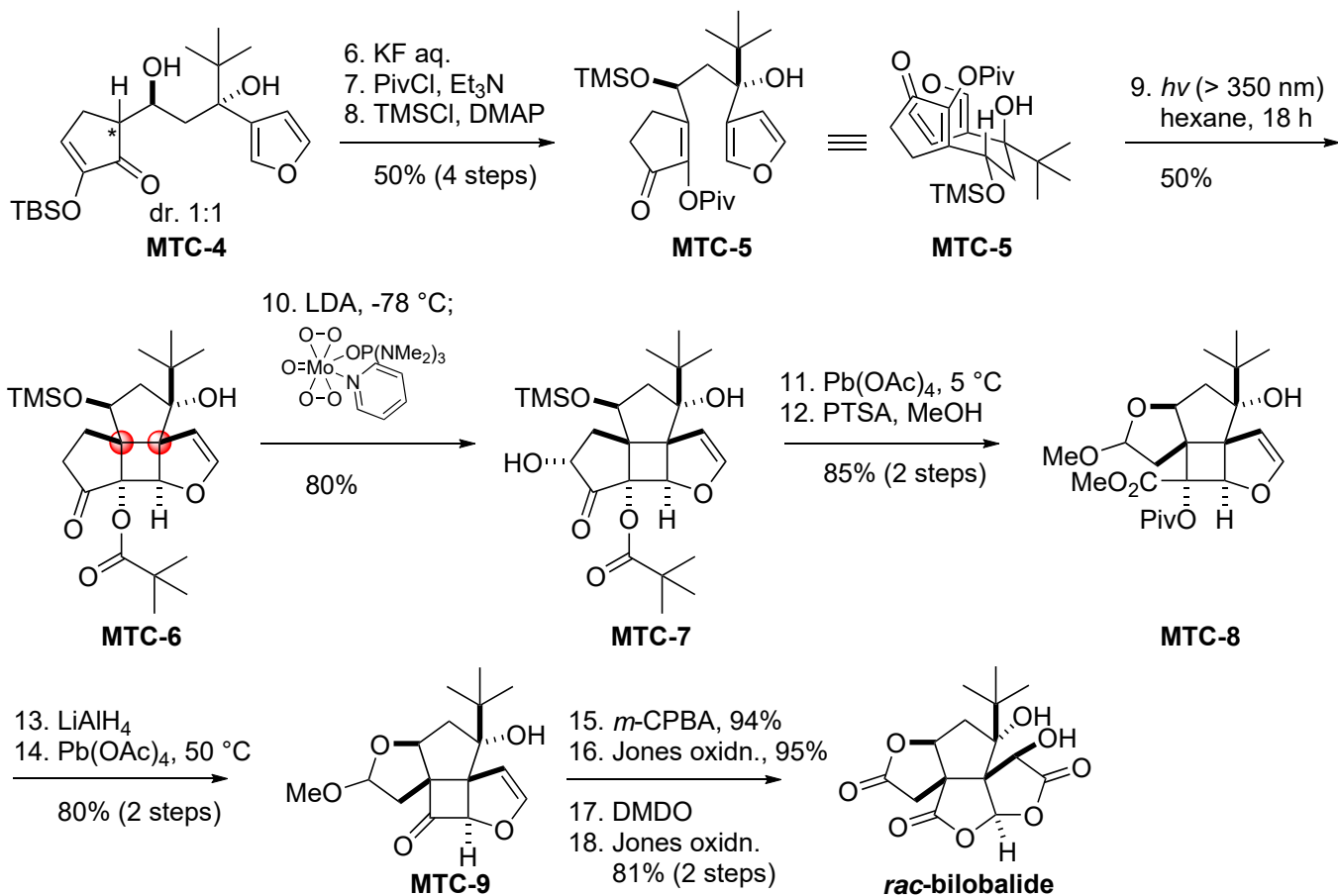
MTC-2

3. LiCH₂CN
 85% (2 steps)
4. DIBAL-H, 56%

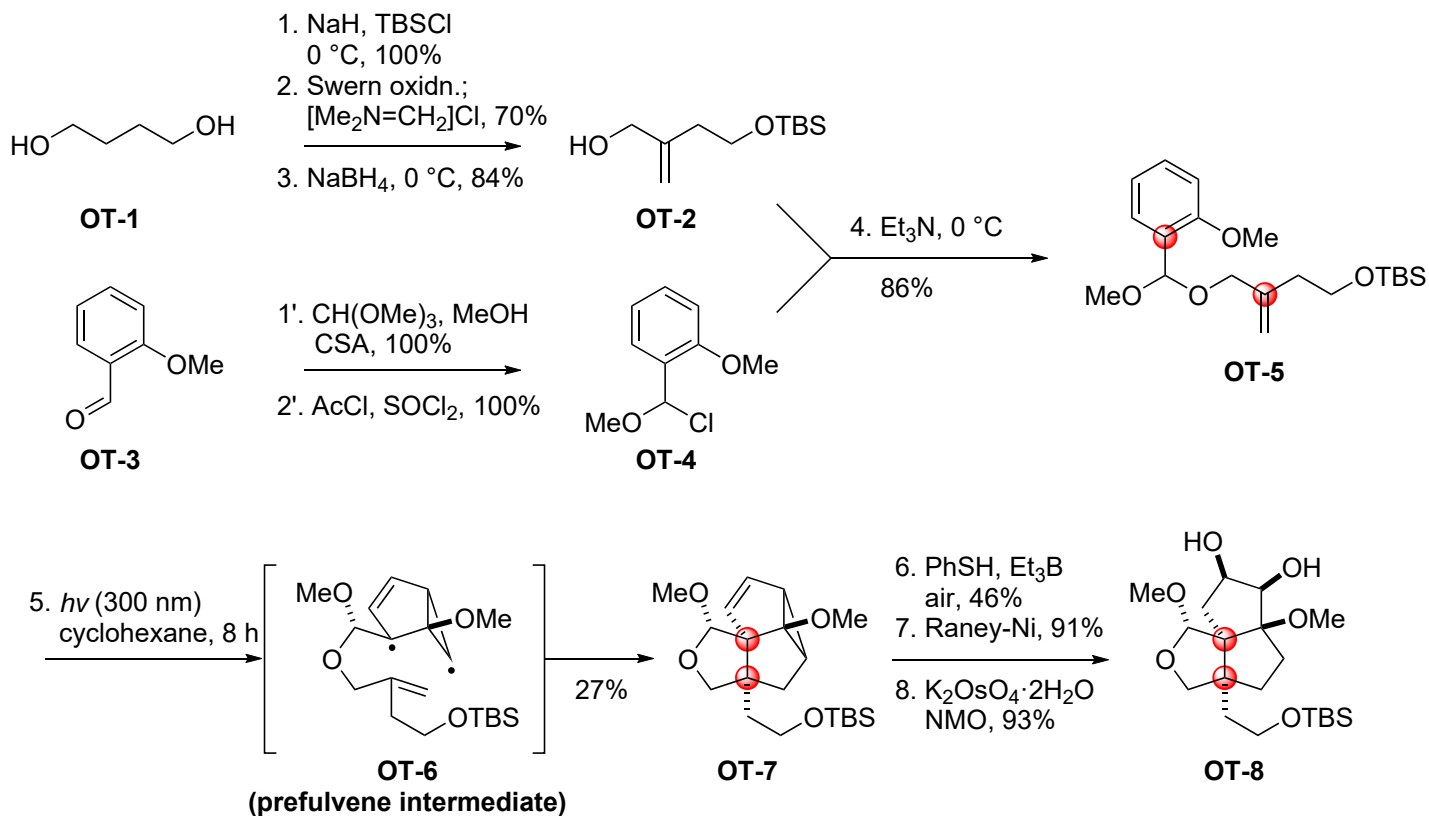


MTC-3

5. MTC-4
 TBSO (2)
 -78 °C, (85%)



Opatz's Synthetic Study_1_Racemic



Our original synthetic plans of (-)-bilobalide are not depicted.