Total Synthesis of Ingenol

Nickel, A.; Maruyama, T.; Tang, H.; Murphy, P. D.;
Greene, B.; Yusuff, N.; Wood, J. L.

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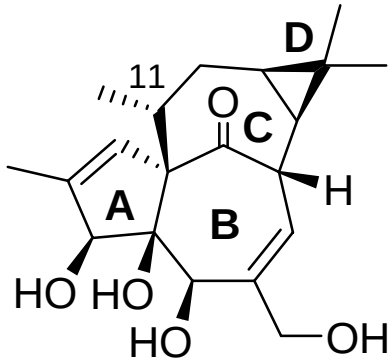
Corey Stephenson

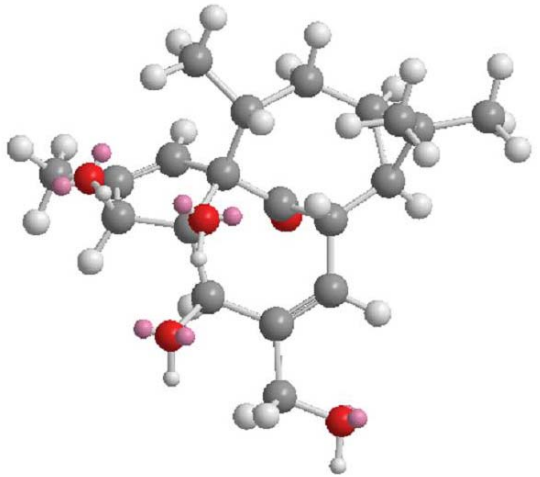
Current Literature Reports 15/1/05

Isolation and Properties

- Isolated in 1968 from *Europhobia ingens*
- Activates protein kinase C
- Potent tumor promoter
- Possesses anti-HIV activity

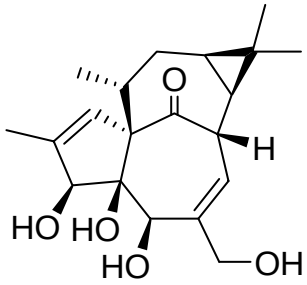


Synthetic Challenges

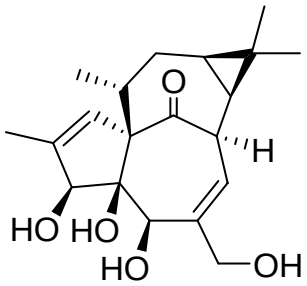


- Highly strained bicyclo[4.4.1]undecane skeleton due to the *inside-outside* stereochemical relationship of the bridgehead.
- Isolated methyl-bearing stereocentre at C11
- Densely functionalized core structure

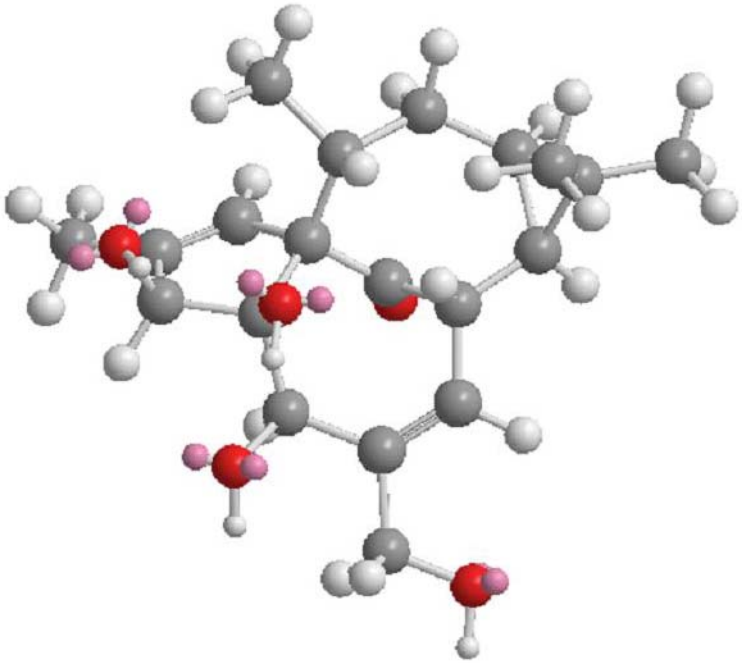
In-out vs. Out-out Bicyclic alkane

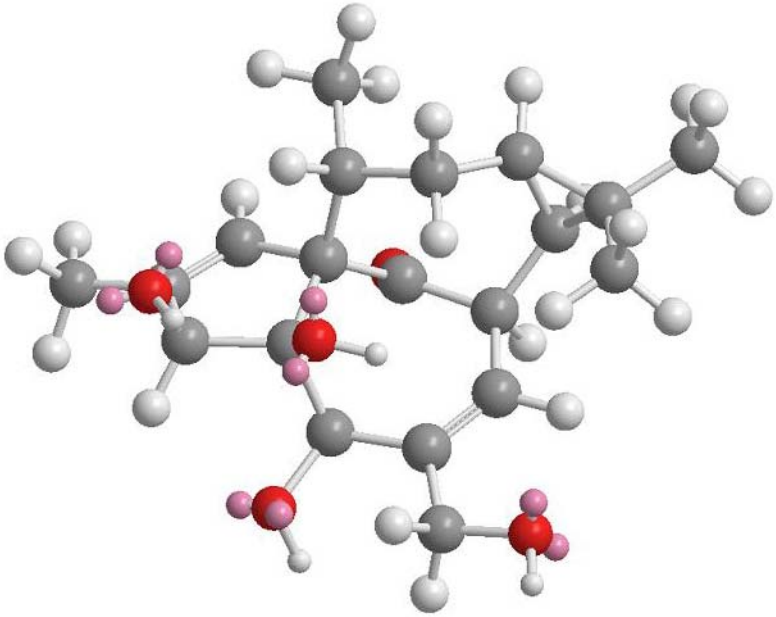


65.2



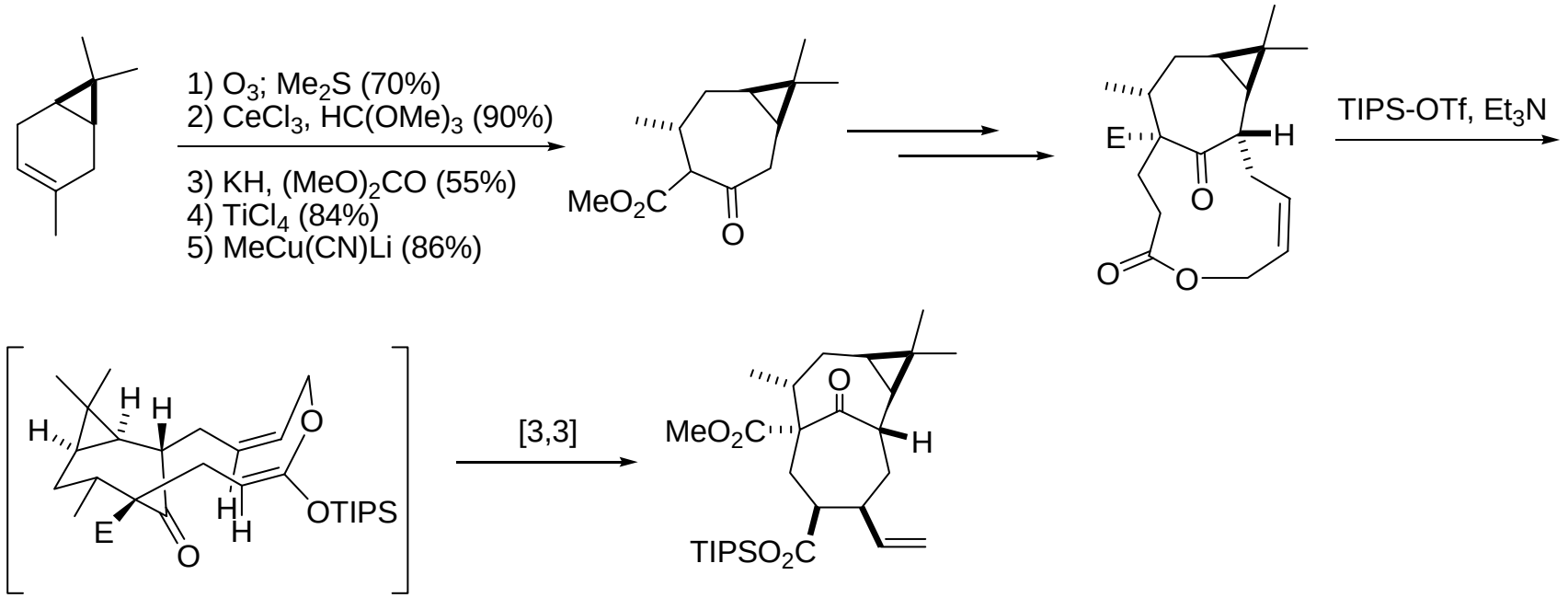
59.6





Funk, R. L.; Olmstead, T. A.; Parvez, M. *J. Am. Chem. Soc.* **1988**, *110*, 3298
For a review on in-out isomerism, see Alder, R.W.; East, S.P. *Chem. Rev.* **1996**, *96*, 2097

Funk's Approach to the Ingenane Core



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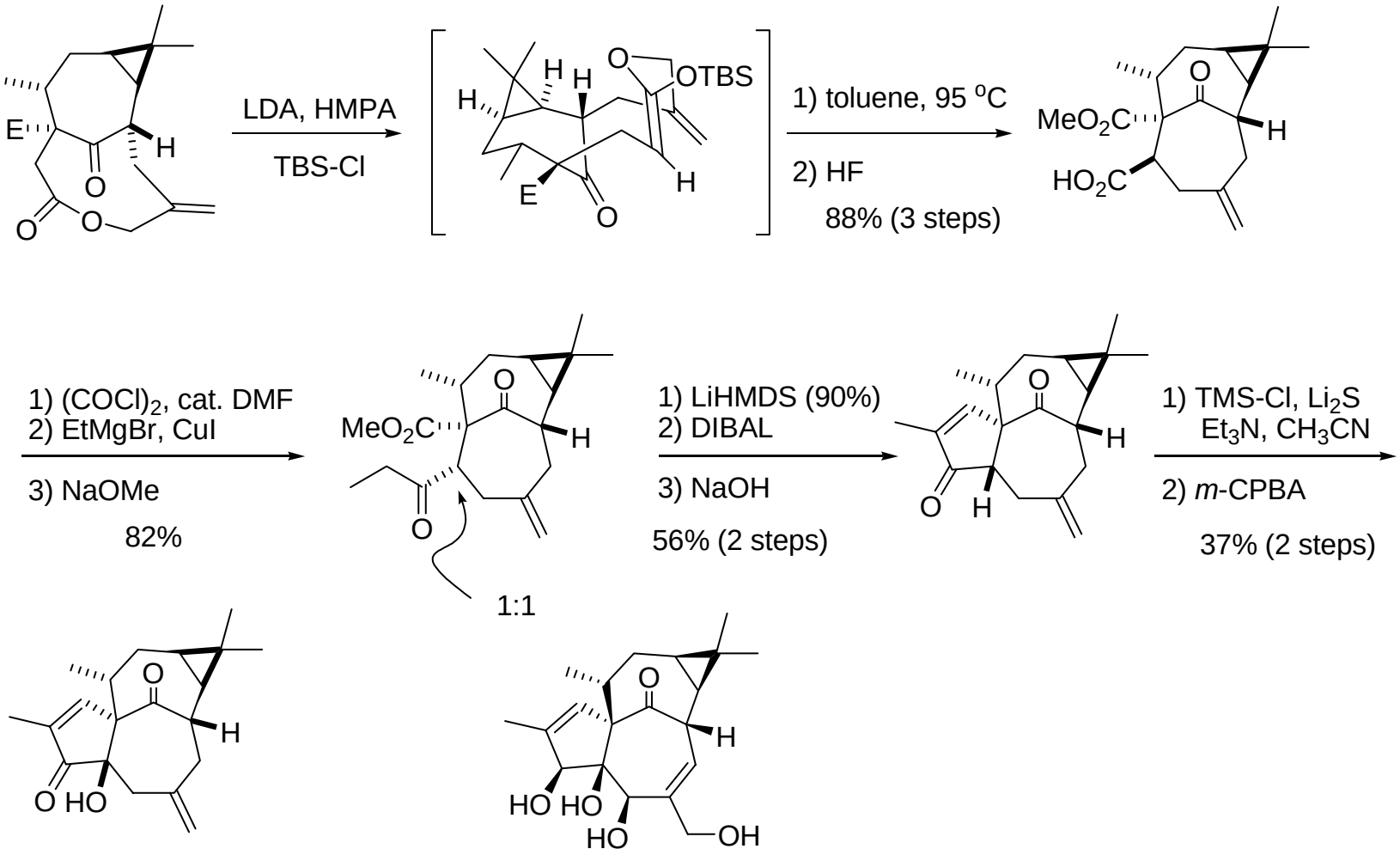
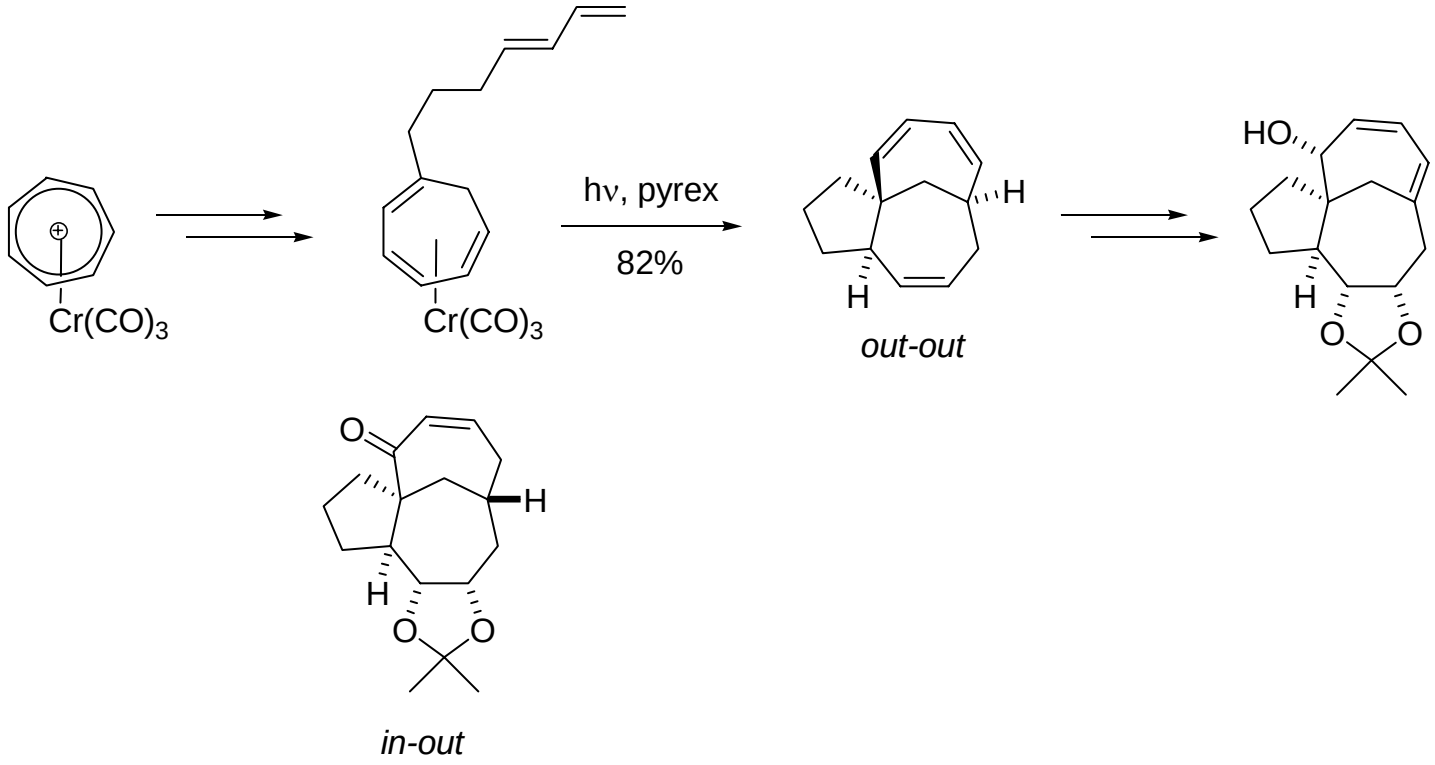


Funk, R. L.; Olmstead, T. A.; Parvez, M.; Stallman, J. B. *J. Org. Chem.* **1993**, *58*, 5873

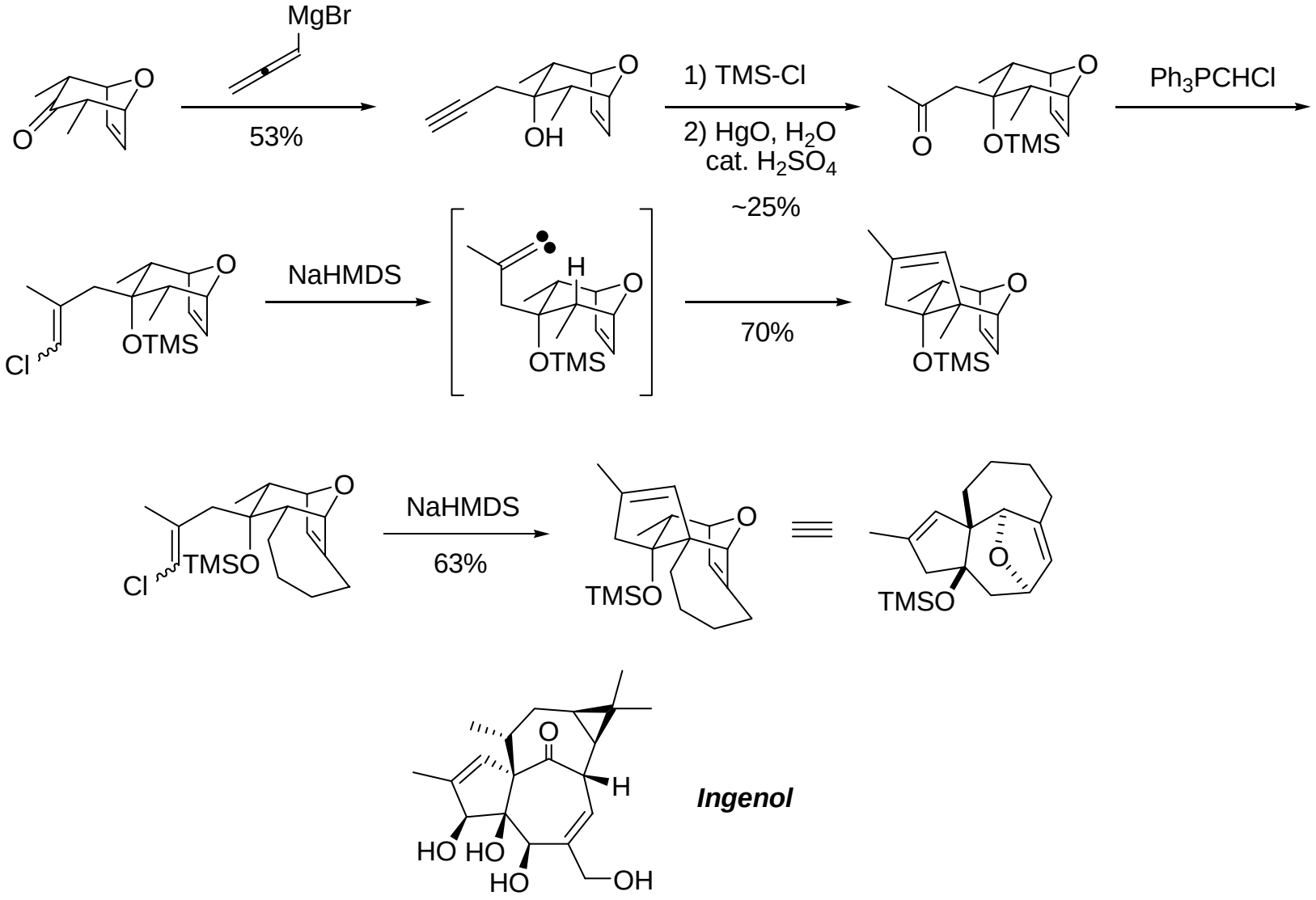
Rigby's Approach to the Ingenane Core



Rigby, J.H.; Hu, J.; Hegg, M.J. *Tetrahedron Lett.* **1998**, *39*, 2265

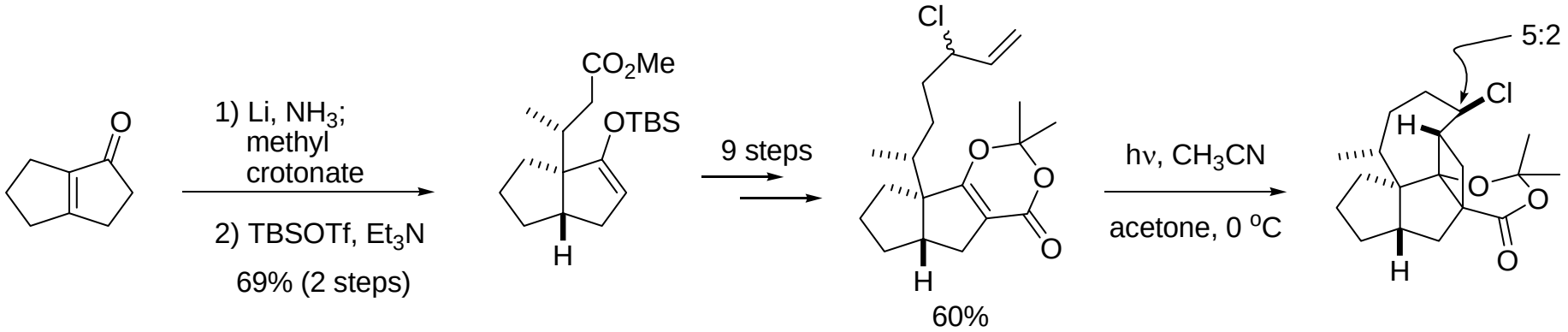
Rigby, J.H.; Bazin, B.; Meyer, J.H.; Mohammadi, F. *Org. Lett.* **2002**, *4*, 799

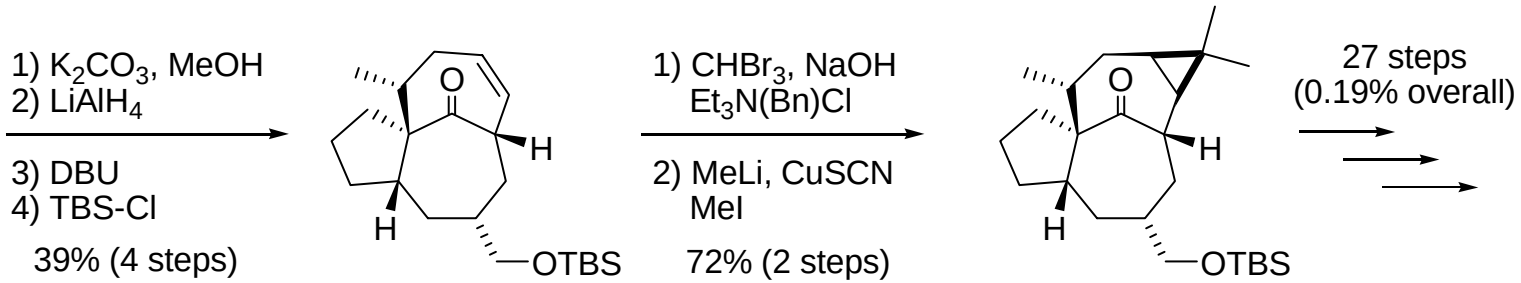
Grainger's Approach to the Ingenane Core



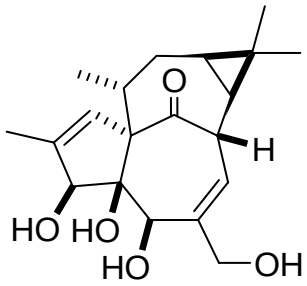
Grainger, R. S.; Owoare, R. B. *Org. Lett.* **2004**, *6*, 2961

Winkler's Total Synthesis of (+/-)-Ingenol





18 steps (3.5% overall)

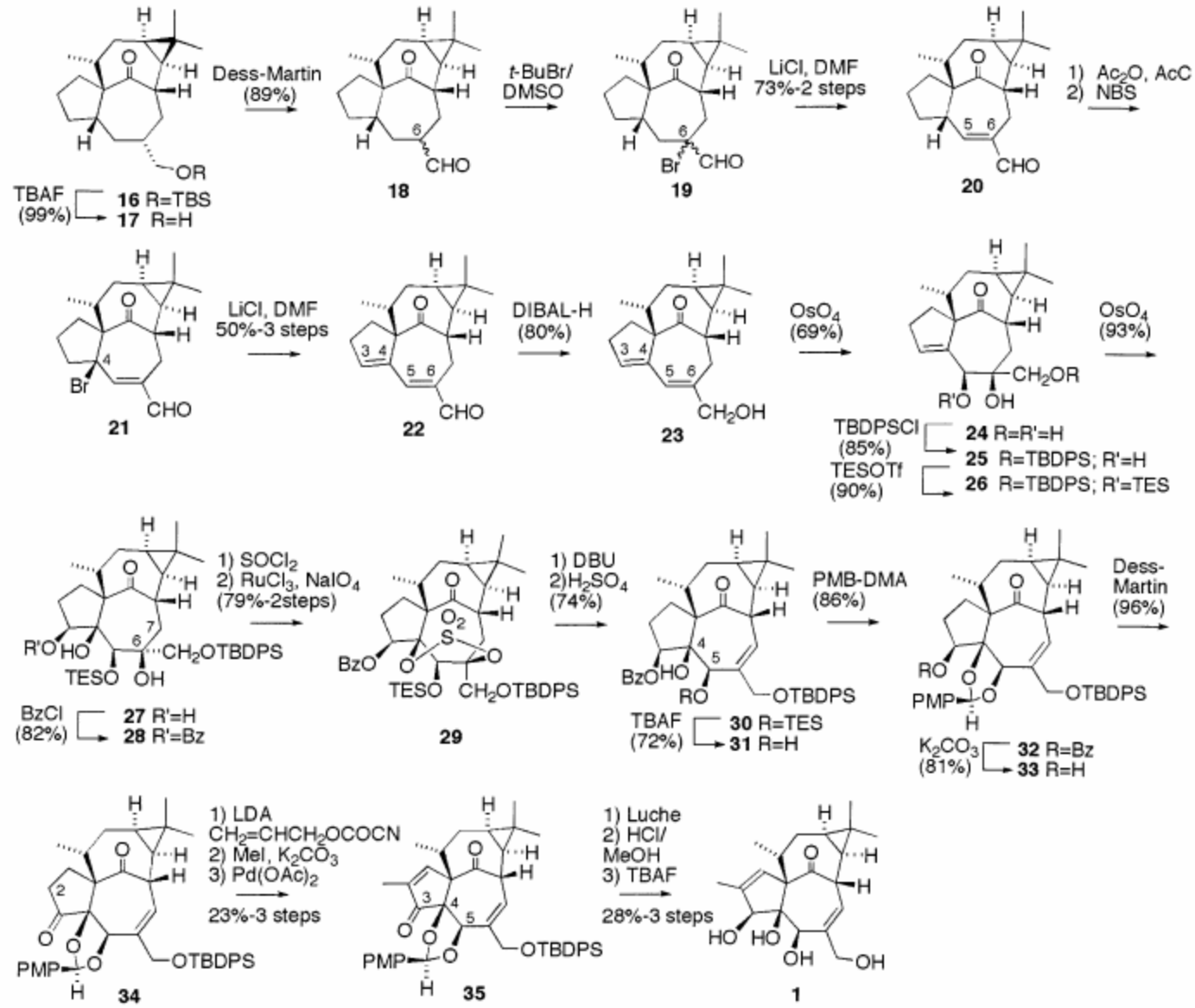


Ingenol

45 steps
(0.007% overall yield)

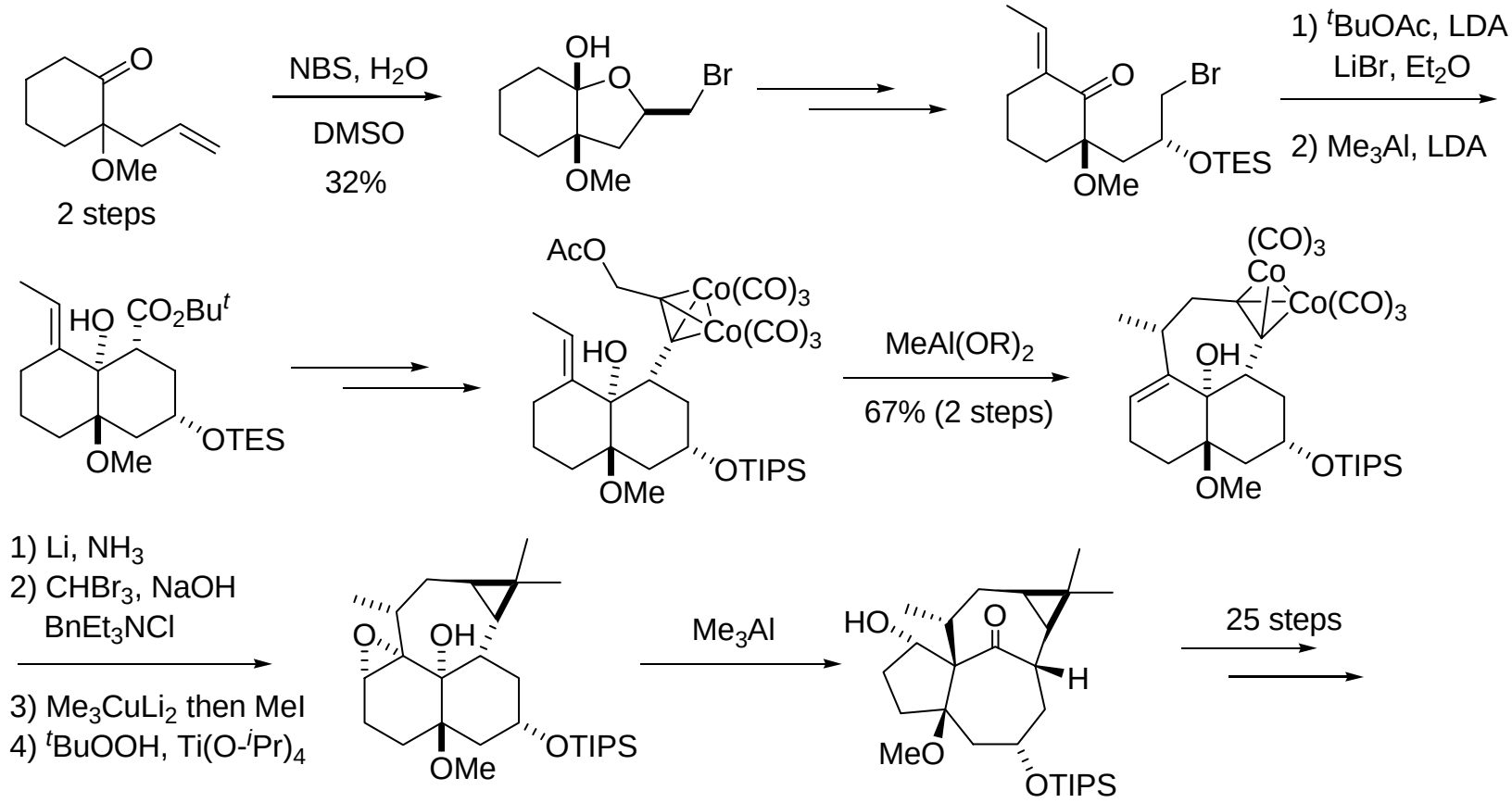
Winkler, J. D. et al *J. Am. Chem. Soc.* **2002**, *124*, 9726

Winkler's Total Synthesis of (+/-)-Ingenol



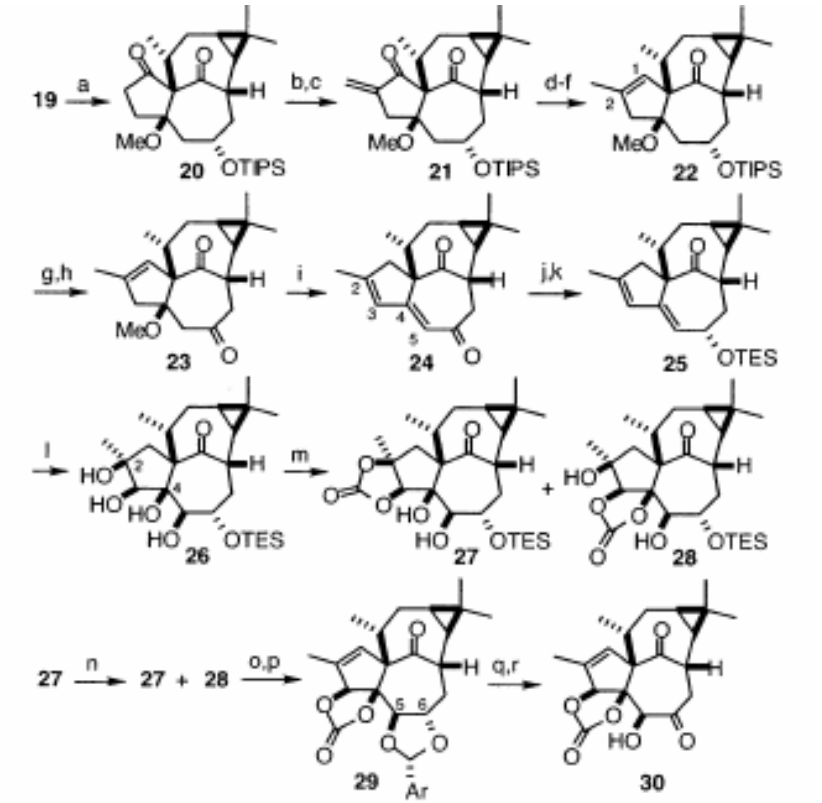
Winkler, J. D. et al *J. Am. Chem. Soc.* **2002**, *124*, 9726

Tanino/Kuwajima's Total Synthesis of (+/-)- Ingenol

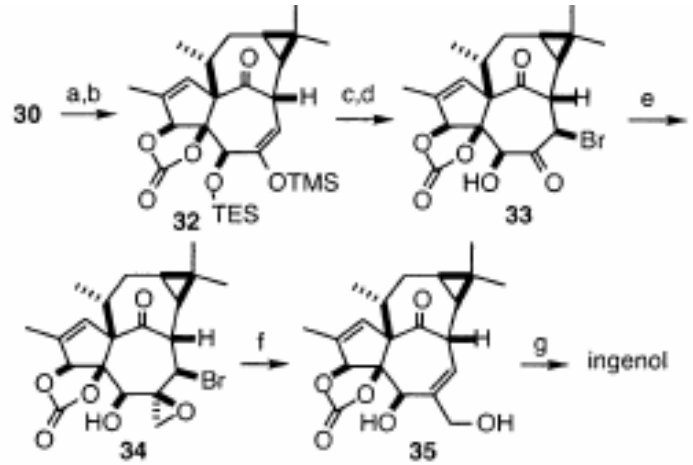


Tanino, K. et al *J. Am. Chem. Soc.* **2003**, *125*, 1498

Tanino/Kuwajima's Total Synthesis of (+/-)- Ingenol



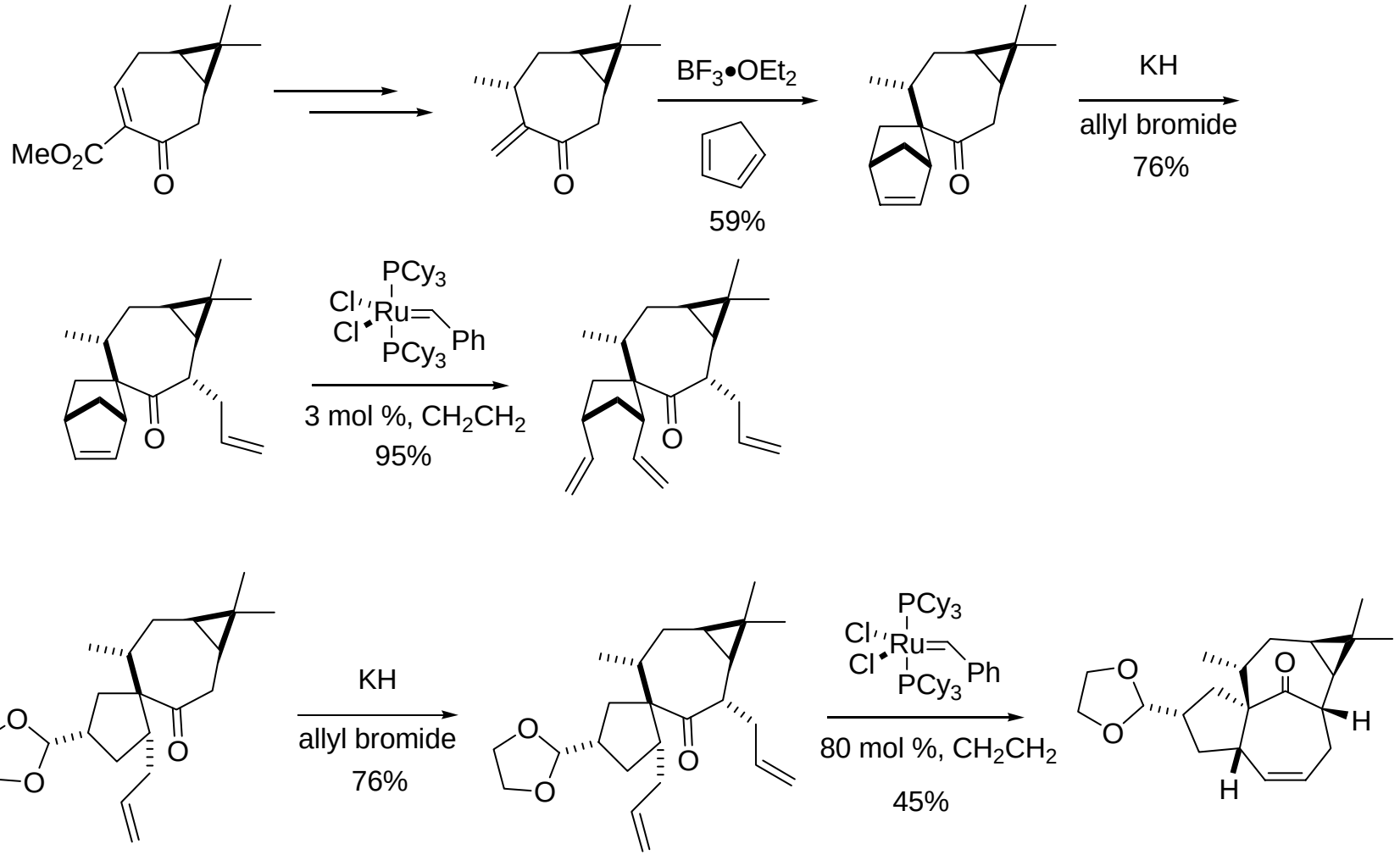
[a] Reagents and conditions: (a) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2 (93%);. (b) $^tBuO(Me_2N)_2CH$, DMF, 100 °C; (c) DIBAL, CH_2Cl_2, MeI, THF (98% in 2 steps); (d) $NaBH_4$, EtOH (95%); (e) DIBAL, CH_2Cl_2; (f) $(CF_3SO_2)_2O$, 2,6-lutidine, DBU, CH_2Cl_2 (83% in 2 steps); (g) TBAF, THF (100%); (h) PDC, CH_2Cl_2 (97%); (i) 1,3,4,6,7,8-hexahydro-1-methyl-2H-pyrimido[1,2-a]pyrimidine, DMF, 120 °C (86%); (j) $NaBH_4$, $CeCl_3$, MeOH−H_2O; (k) TESCl, imidazole, DMF (99% in 2 steps); (l) OsO_4, pyridine, ether, then $NaHSO_3$, H_2O (59%); (m) 1,1′-carbonyldiimidazole, toluene (**27**: 76%, **28**: 18%); (n) 4-(dimethyl-amino)pyridine, toluene, 100 °C; (**27**: 72%, **28**: 27%) (o) *p*-$MeOC_6H_4CH(OMe)_2$, CSA, DMF (93%); (p) $SOCl_2$, pyridine; (q) AcOH−H_2O (96% in 2 steps); (r) Me_2S, NCS, toluene (75%).



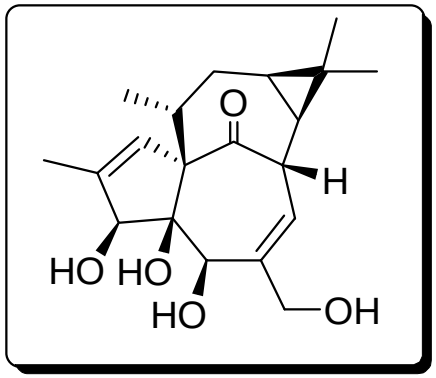
[a] Reagents and conditions: (a) TESOTf, 2,6-lutidine, CH_2Cl_2; (b) TMSCl, Et_3N, LDA, THF; (c) NBS, CH_2Cl_2; (d) HF, CH_3CN; (e) CH_2I_2, MeLi, THF (39% in 5 steps); (f) Zn, NH_4Cl, THF−H_2O (91%); (g) KOH, MeOH (89%).

Tanino, K. et al *J. Am. Chem. Soc.* **2003**, *125*, 1498

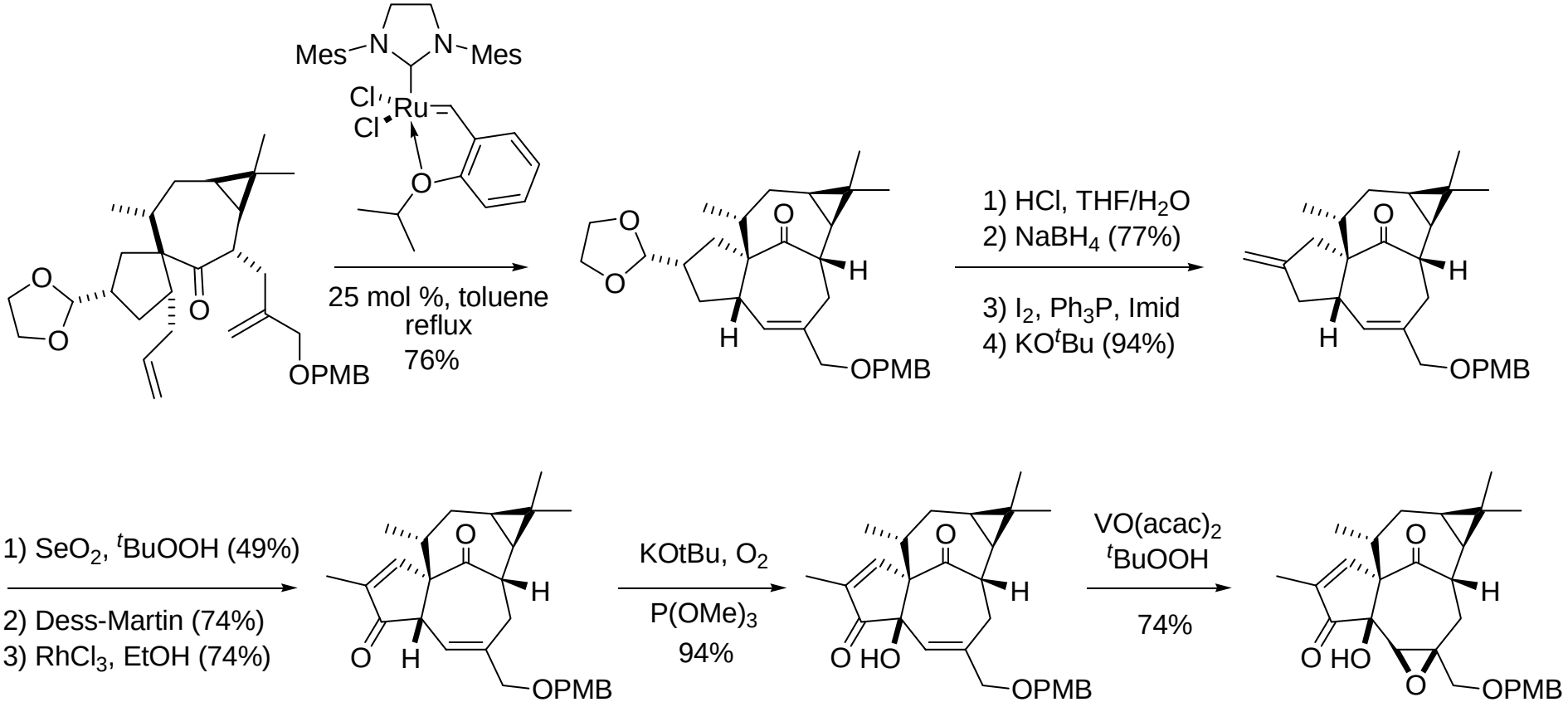
Wood's Asymmetric Synthesis of Ingenol



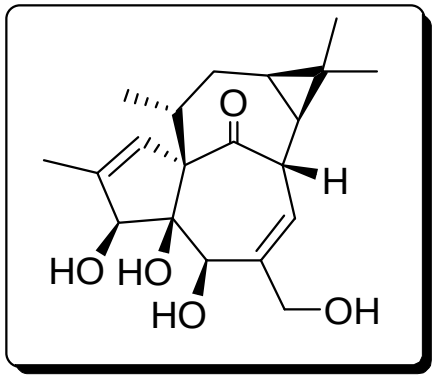
Tang, H.; Yusuff, N.; Wood, J.L. *Org. Lett.* **2001**, *3*, 1563



Wood's Asymmetric Synthesis of Ingenol



Nickel, A. et al *J. Am. Chem. Soc.* **2004**, *126*, 16300



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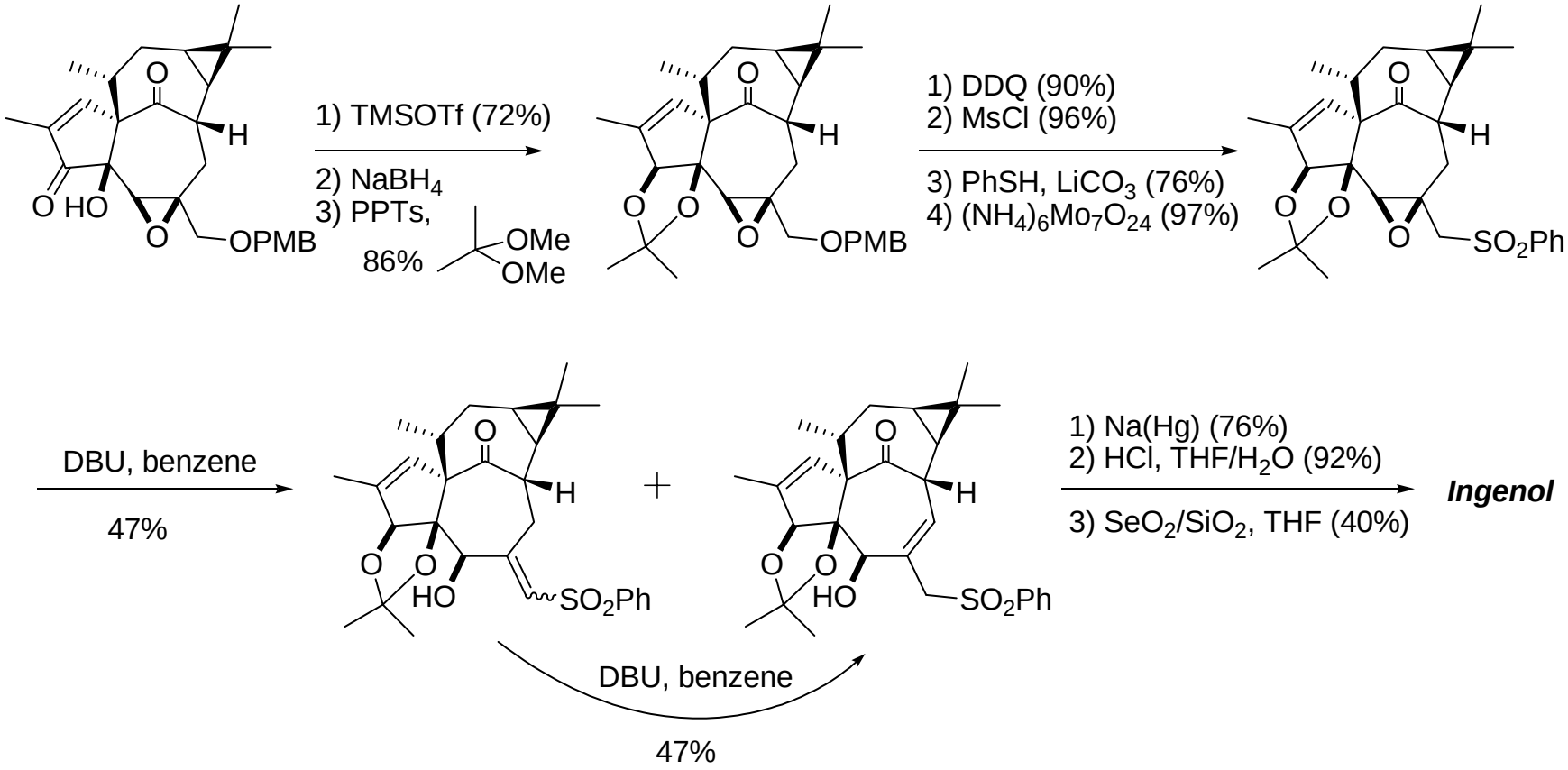

Nickel, A. et al *J. Am. Chem. Soc.* **2004**, *126*, 16300

Summary

- Winkler (2002) – racemic (45 steps, 0.007% overall yield)
- Kuwajima/Tanino (2003) – racemic (46 steps, 0.03% overall yield)
- Kigoshi (2004) – Formal asymmetric synthesis (36 steps, 0.01% overall yield based upon Winkler's route *J. Org. Chem.* **2004**, *69*, 7802)
- Wood (2004) – Asymmetric total synthesis (37 steps, 0.002% overall yield)