Christian Gloor
Journal Club Group Meeting
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14-Step Synthesis of (+)-Ingenol from (+)-3-Carene

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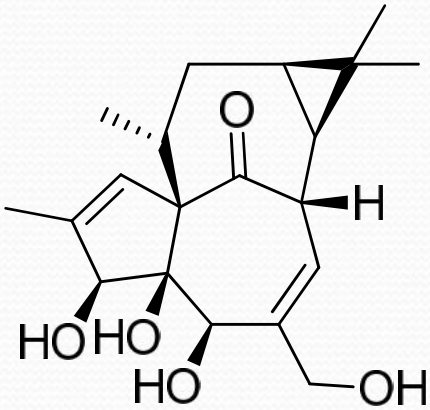
Science **2013**, *341*, 878-882

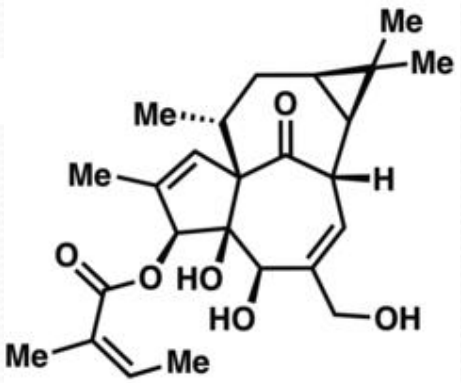
Isolation, Structure and biological activity

- Ingenol was first isolated from *Euphorbia ingens* in 1968



- Unique *in,out*-[4.4.1]bicycloundecane core
- Ingenol esters possess important anticancer and anti-HIV activity.

Isolation, Structure and biological activity

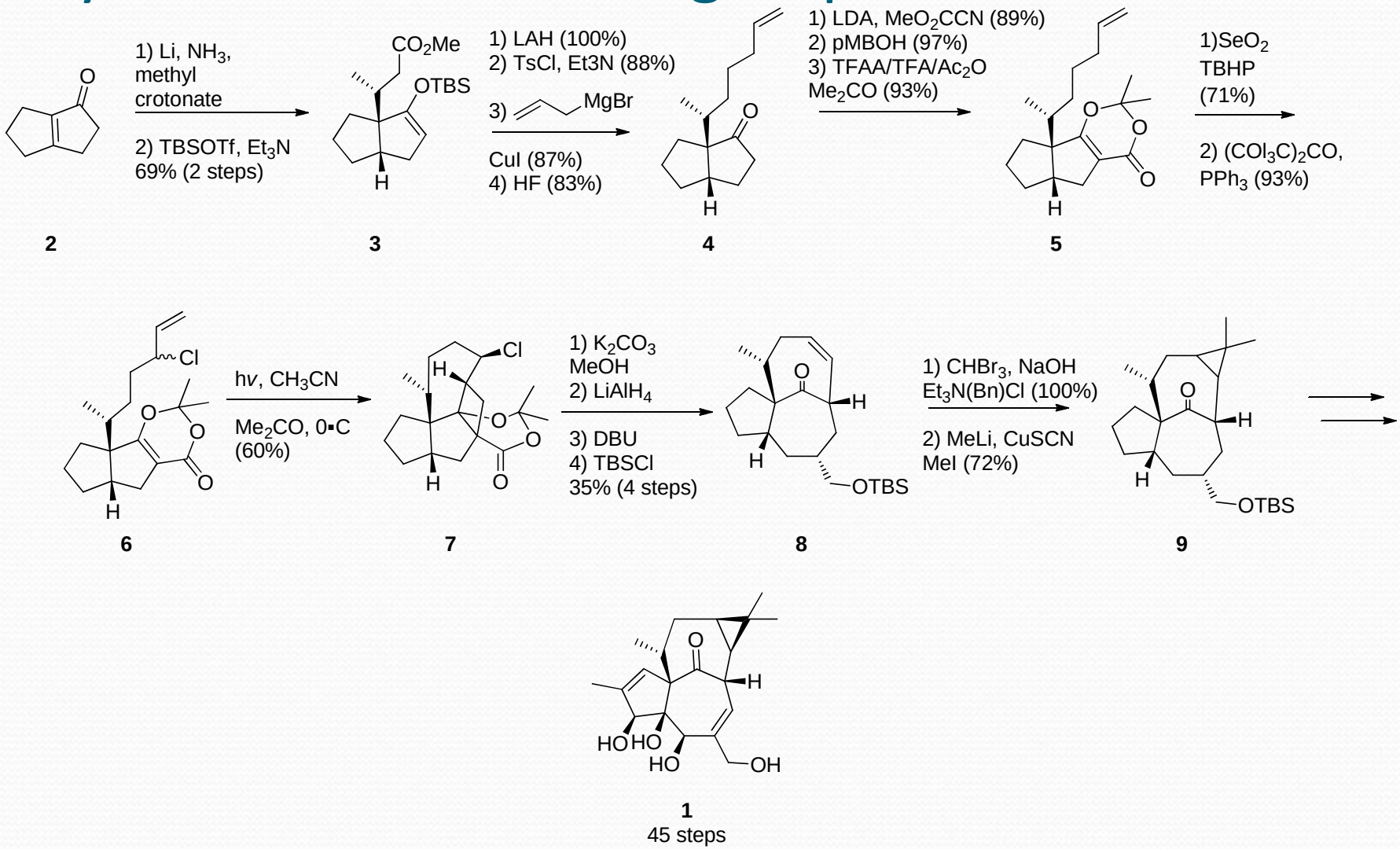


ingenol mebutate
(Picato®)

- *e.g. Ingenol mebutate was recently approved as a first-in-class treatment of actinic keratosis (precancerous skin condition) and can be synthesised from Ingenol.*

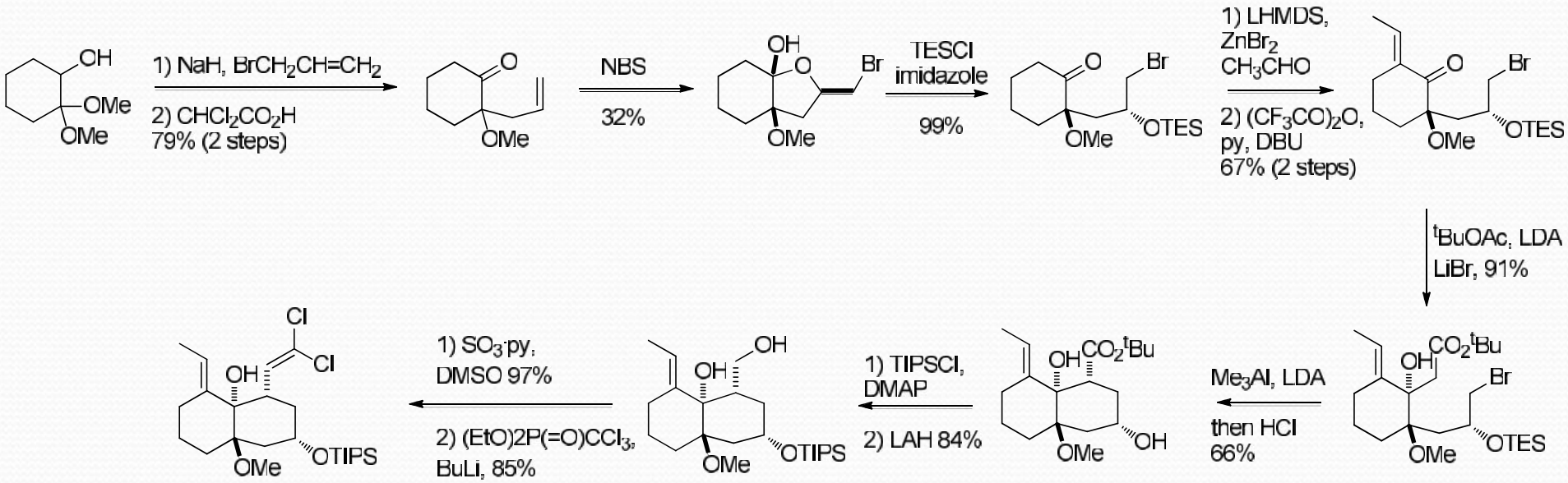
- *Synthesis of Ingenol is requested since the isolation of the natural product leads to a lot of waste (1.1mg/kg).*

Synthesis of Winkler's group



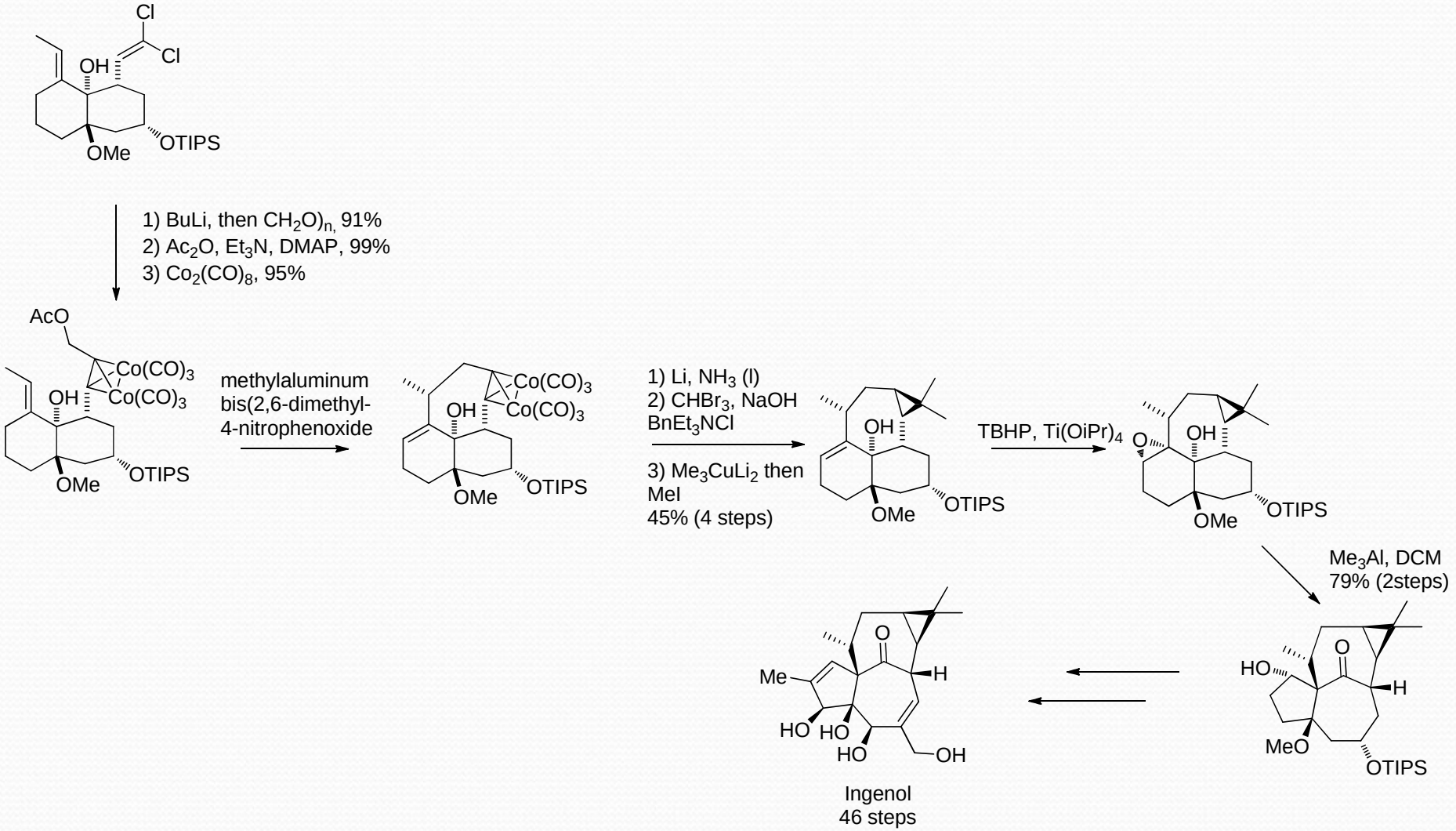
Winkler, J. D.; Rousee, M. B.; Greaney, M. F.; Harrison, S. J.; Jeon, Y. T. *J. Am. Chem. Soc.* **2002**, *124*, 9726-9728

Synthesis of Kuwajima's group



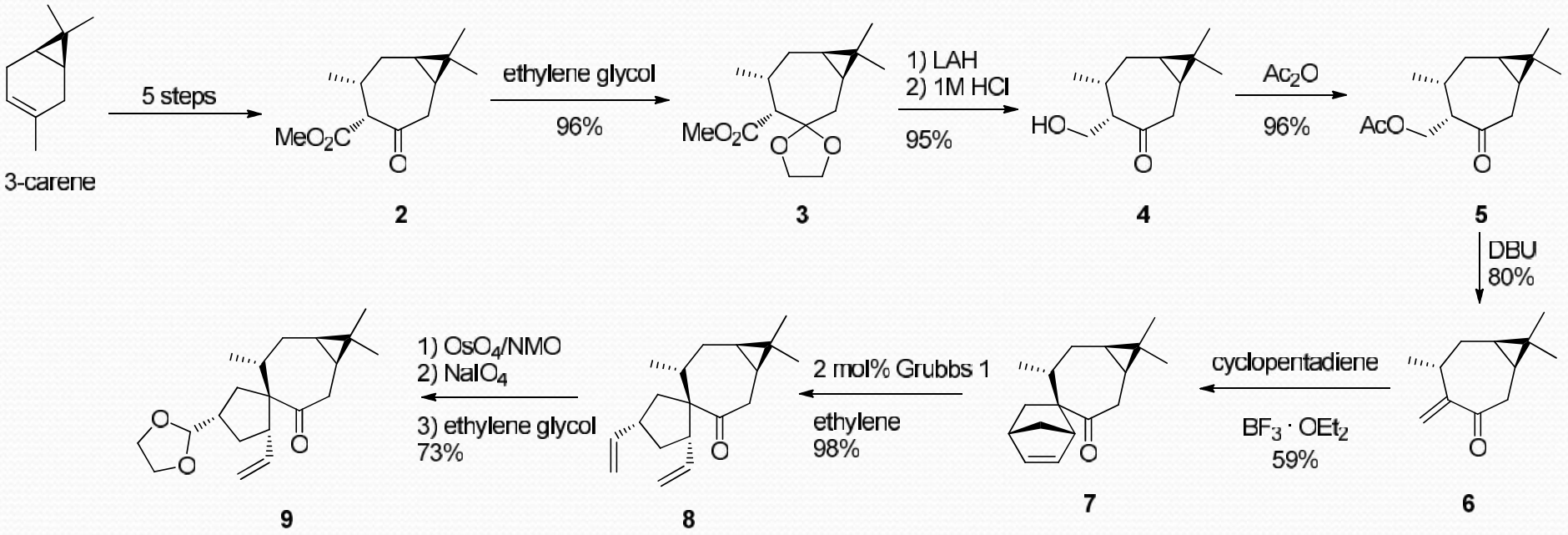
Tanino, K.; Onuki, K.; Miyashita, M.; Nakamura, T.; Takahashi, Y.; Kuwajima, I. *J. Am. Chem. Soc.* **2003**, *125*, 1498-1500

Synthesis of Kuwajima's group



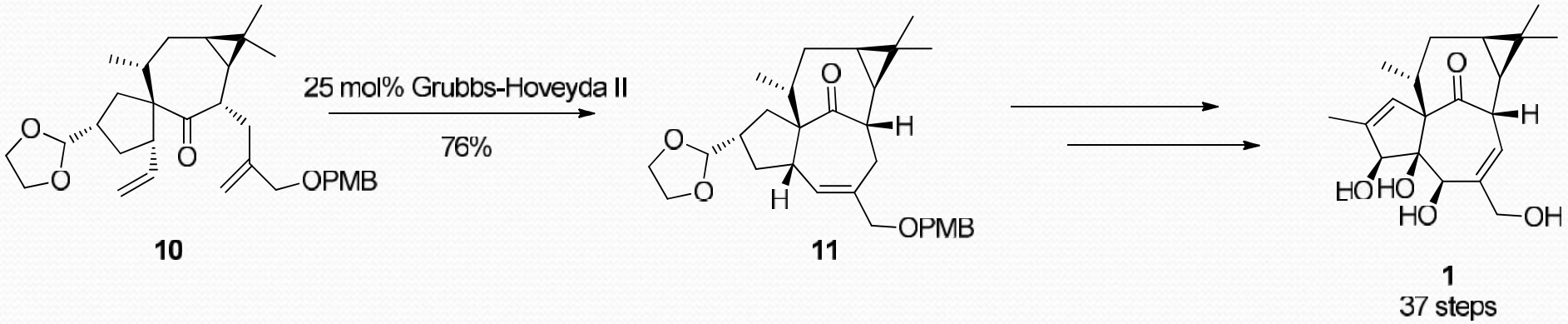
Tanino, K.; Onuki, K.; Miyashita, M.; Nakamura, T.; Takahashi, Y.; Kuwajima, I. *J. Am. Chem. Soc.* **2003**, *125*, 1498-1500

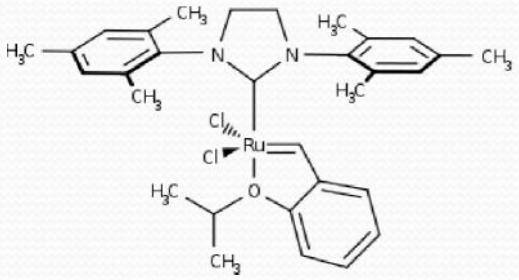
Synthesis of Wood's group



Tang, H.; Yusuff, N.; Wood, J.L. *J. Am. Chem. Soc.* **2001**, *3*, 1563-1566

Synthesis of Wood's group

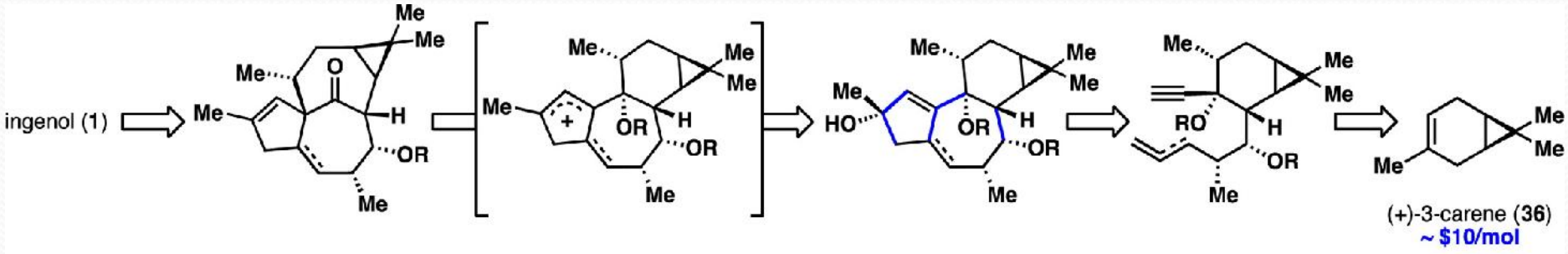




Grubbs-Hoveyda II

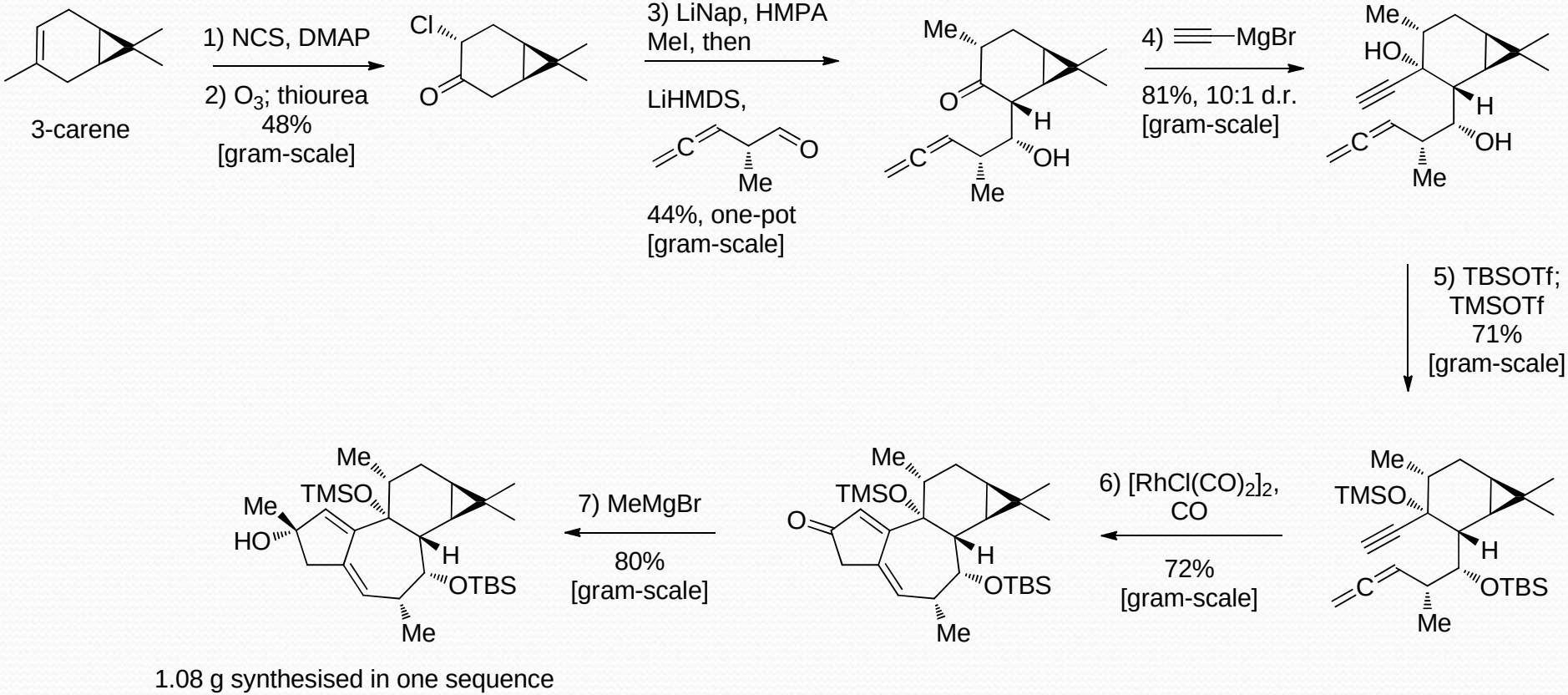
Nickel, A.; Maruyama, T.; Murphy, P.D.; Greene, B.; Yusuff, N.; Wood, J.L. *J. Am. Chem. Soc.* **2004**, *126*, 16300-16301

Retrosynthetic approach of Baran's group



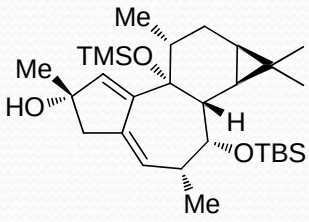
McKerrall, S. J.; Jørgensen, L.; Kuttruff, C. A.; Ungeheuer, F.; Baran, P. S. *J. Am. Chem. Soc.* **2014**, *136*, 5799-5810

Synthesis of Baran's group

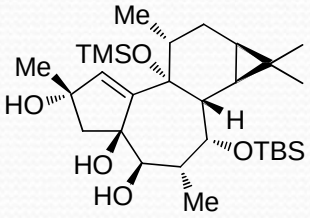


1.08 g synthesised in one sequence

Synthesis of Baran's group

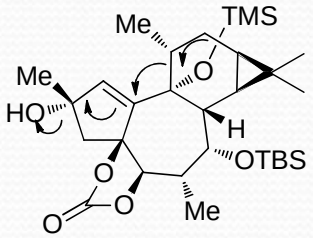


8) OsO_4



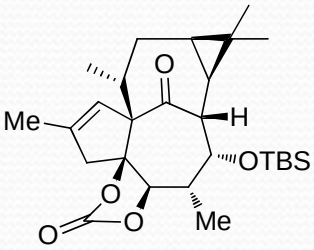
9) CDI

68% (2 steps)

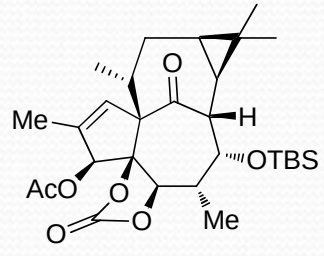


10) $BF_3 \cdot Et_2O$

80%

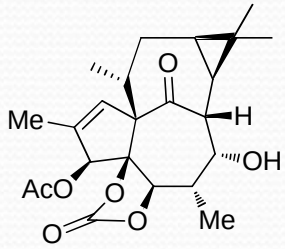


11) SeO_2, then Ac_2O 59%



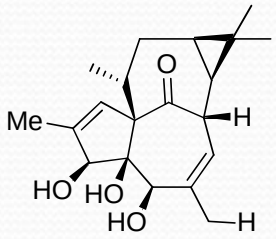
12) HF

90%



13) Martin's sulfurane,

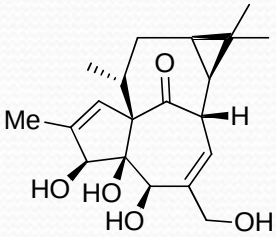
then NaOH 81%



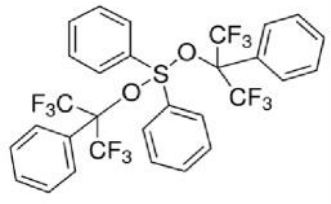
20-deoxyingenol

14) SeO_2, HCO_2H

76%



Ingenol
14 steps
1.2% overall yield



Martin's sulfurane
Dehydrating agent

Conclusion

- total synthesis was achieved with 14 linear steps and an overall yield of 1.2%

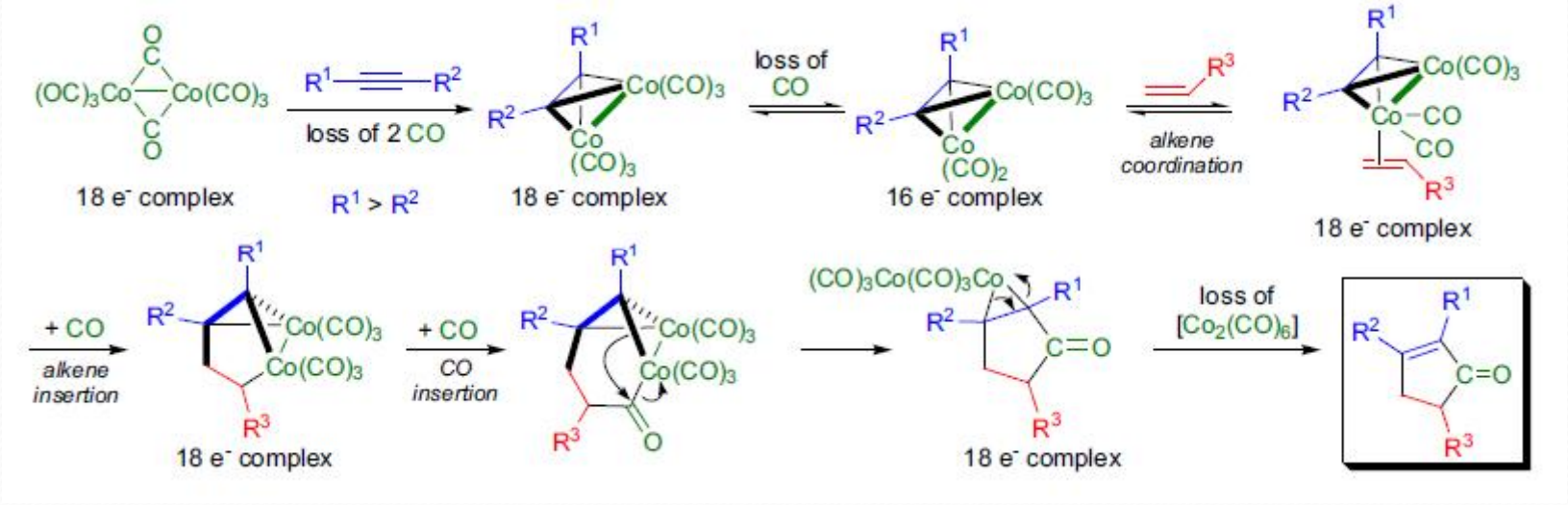
- A catalytic allenic Pauson-Khand reaction producing the core carbon skeleton

- A vinylogous pinacol rearrangement setting the *in,out*-stereoselectivity

- Use of stoichiometric quantities toxic oxidants (OsO_4 and SeO_2) is a limitation

Thank you for your attention

Pauson-Khand reaction



Pinacol rearrangement