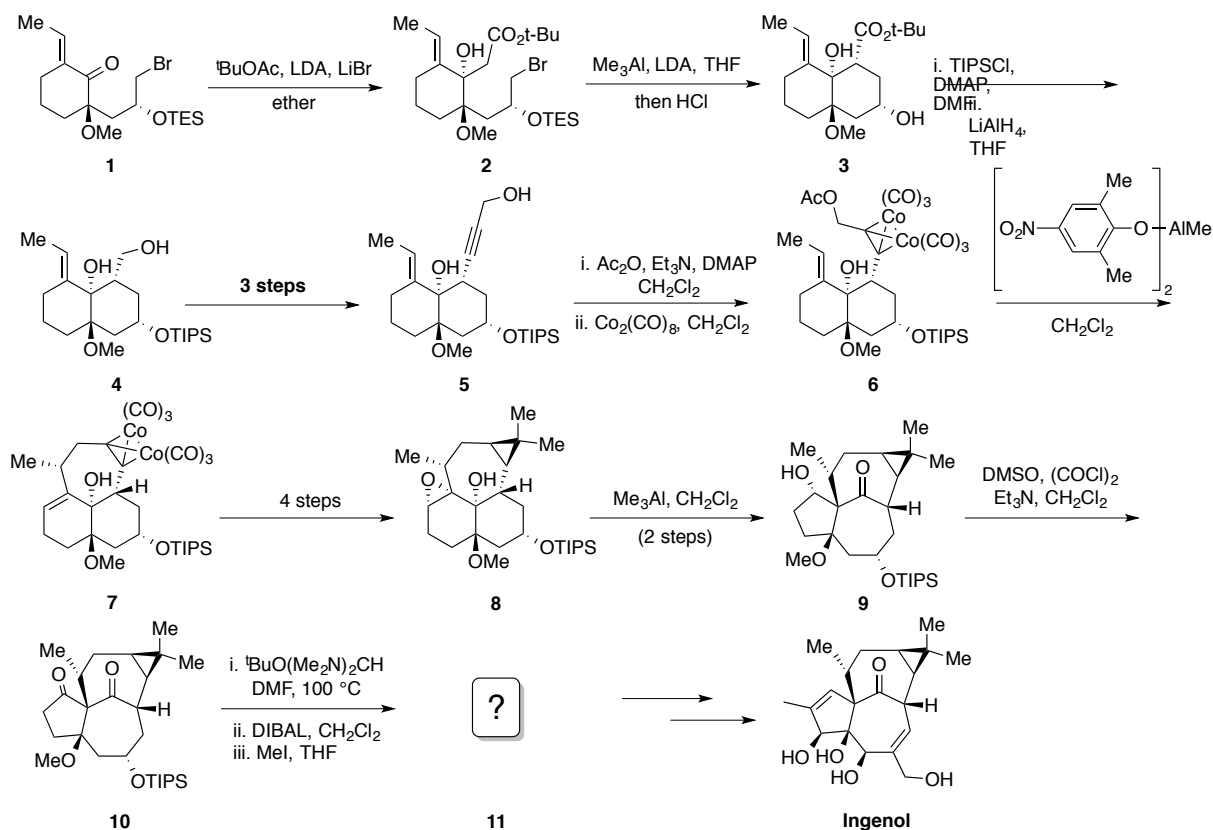


Total Synthesis of Ingenol



Questions

1. Explain the stereoselectivity observed for the formation of compounds **2** and **3**.
2. Give the three missing steps between **4** and **5** (not a substitution).
3. Explain the mechanism for the formation of **7**. Can you suggest an alternative product which is formed when a weaker Lewis acid is used?
4. Give the mechanism for the formation of **9**, and name the reaction.
5. Give the missing compound **11**, and the mechanisms of the three steps yielding to it.

Solutions

Article:

K. Tanino, K. Onuki, K. Asano, M. Miyashita, T. Nakamura, Y. Takahashi, I. Kuwajima, *J. Am. Chem. Soc.*, **2003**, *125* (6), pp 1498–1500. DOI: 10.1021/ja029226n - **Total Synthesis of Ingenol**

- Formation of compound **2**: the conformation of the α -methoxyketone would be restricted by forming a five-membered chelate ring. The lithium enolate of *tert*-butyl acetate would then attack the carbonyl group from the opposite side of the side chain (Figure 1, A).
 - Formation of compound **3**: the absence of trimethylaluminium during the reaction failed to give compound **3**. Thus, it was supposed that the formation of a six-membered cyclic aluminium enolate intermediate would be essential for the stereoselective cyclization reaction (Figure 1, B).

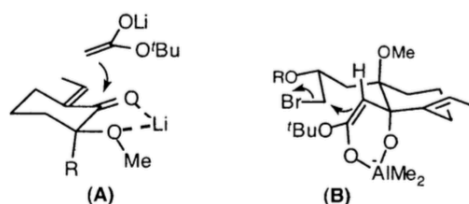
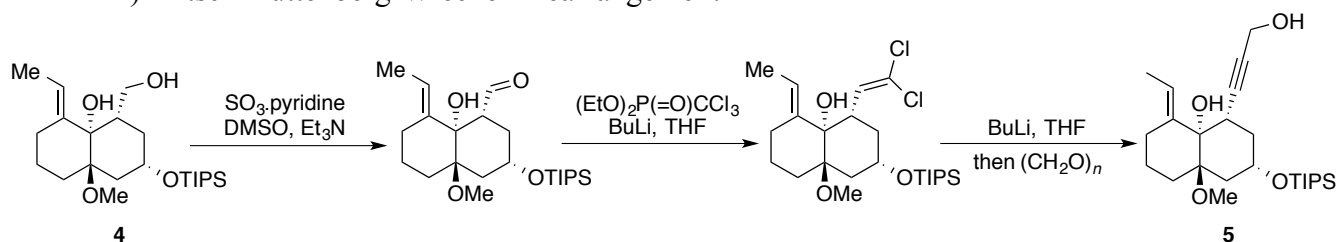
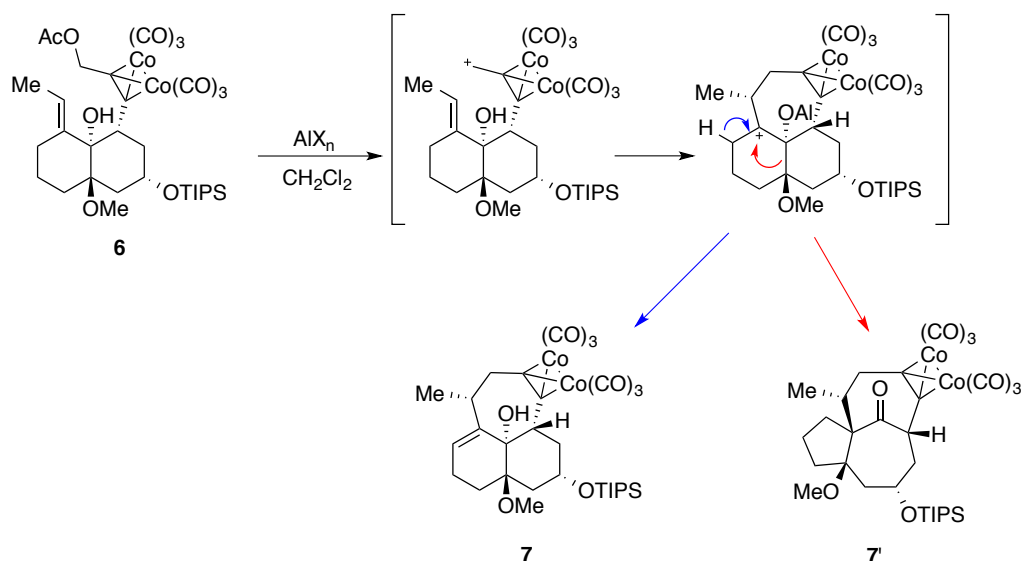


Figure 1. Suggested intermediates of the stereoselective C–C bond-forming reactions.

- Missing steps: i) Parikh-Doering Oxidation; ii) Horner-Wadsworth-Emmons Reaction; iii) Fritsch-Buttenberg-Wiechell Rearrangement



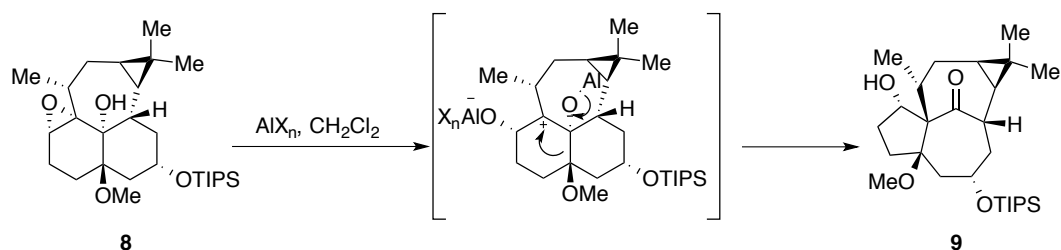
- Mechanism for the formation of compound **7**:



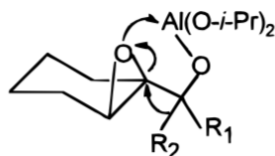
Under the influence of methylaluminium bis(2,6-dimethyl-4-nitrophenoxide), cobalt complex **6** underwent a cyclization reaction to afford allyl alcohol **7**. However, by using a lower Lewis acidic aluminium reagent, the formation of **7'** could have been observed.^[1]

^[1] T. Nakamura, T. Matsui, K. Tanino, I. Kuwajima, *J. Org. Chem.* **1997**, *62*, 3032 – 3033

4. Mechanism for the formation of compound **9**:



Aluminium complex would coordinated first with epoxy oxygen (see scheme below), facilitating a bond cleavage between this oxygen and the crowded quaternary carbon center, forming the C-carbocation intermediate.^[2]



^[2] Y. Qiang Tu, L. Dong Sun, P. Zhen Wang, *J. Org. Chem.* **1999**, *64*, 629 – 633

5. • Mechanisms of the three steps and structure of compound **11**:

