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14-Step Synthesis of (+)-Ingenol from (+)-3-Carene

Lars Jørgensen, Steven J. McKerrall, Christian A. Kuttruff, Felix Ungeheuer,
Jakob Felding, Phil S. Baran

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1. Introduction

1-1. Ingenol

- Ingenol (Figure 1), one of the diterpenoid, was isolated from *Euphorbia ingens* in 1968 by Hecker.[1]
- Ingenol has strained unique C-8/C-10 "*in, out*" trans intrabridgehead structure of BC ring system.
- Ingenol mebutate [Picato] was approved as treatment for actinic keratosis (日光角化症).

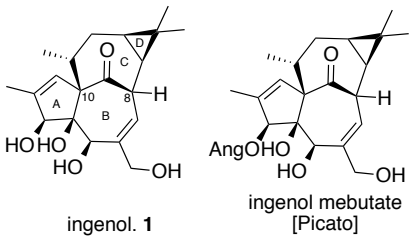


***Figure* 1.** Structure of ingenol and Picato

- Currently the supply of Picato and is limited to direct isolation (1.1 mg per kg of *E. peplus*)[2] and the supply of ingnol is also limited.

  ⇒ stable supply of ingenol is required

1-2. Author's Motivation

- Many of natural products were currently provided by bioengineering such as plant cell culture or collaborations between genetic engineering and chemical synthesis.

  ⇒ widely believed bioengineering is superior to organic synthesis in terpenoids.
- Biosynthetic pathway of ingenol is largyly unknown so engineering biosynthesis faces problem.
- Previously, 3 total synthesis were reported.

  ⇒ over 37 steps and under 0.1% yield.
- Author presented this case study that chemical synthesis is the best way to produce terpenoids because of advantage of analog synthesis.

1-3. Author's strategy

- Author focused on that biosynthesis of terpenoid often occurred "two-phase" process means first cyclase and second oxidase phase.[3]

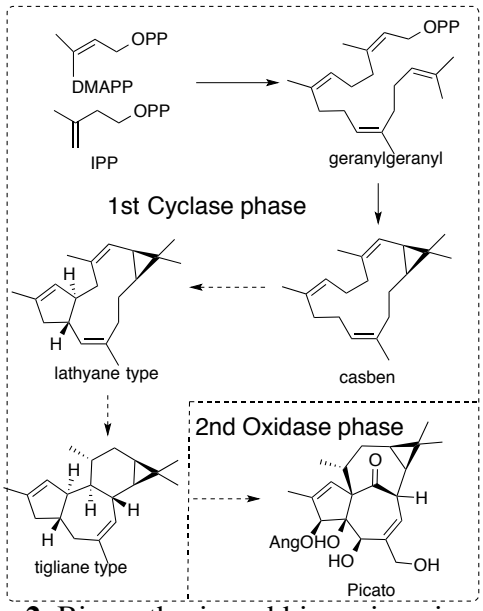


Figure 2. Biosynthesis and bioengineering of ingenane diterpenoids

⇒ author had inspiration from only known key intermediate “casben” in biosynthesis and extrapolate following cyclizations and generate putative “tigliane” skeletons (Figure 2).

- To convert ingenane skeleton, pinacol rearrangement was chosen for key reaction.

  ⇒ however it was reported that the revers reaction is thermodynamically stable [4]

  ⇒ overcome to this problem, previously strain epoxide structure enable this rearrangement [5] (Scheme 1)

  ⇒ optimized temperature and steric hindrance would enable this arrangement

- Cyclase phase was started cheap (+)-3-carene ($ 10.20/mol) as a stereochemistry-controlling factor (Figure 3).

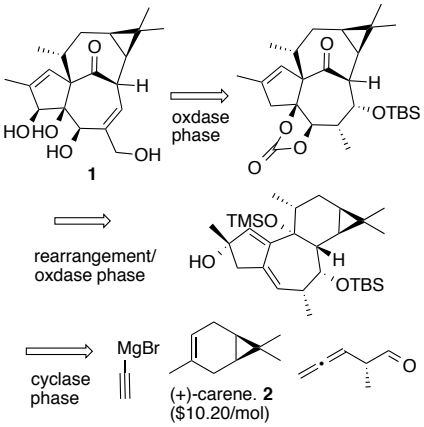
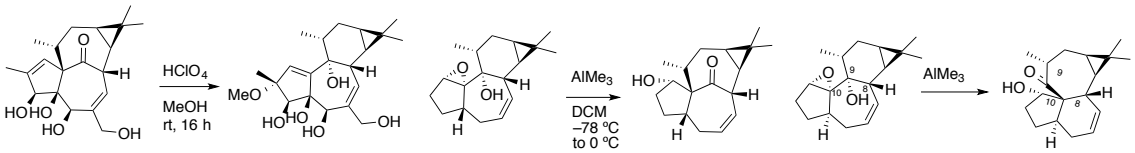


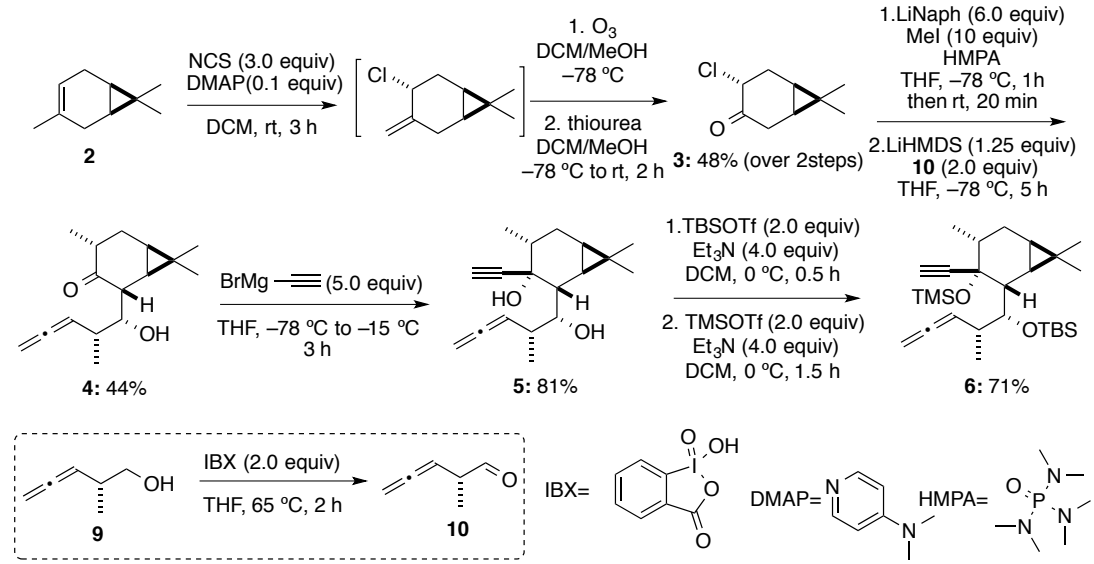
Figure 3. Retrosynthetic analysis of ingenol



Scheme 1. Pinacol rearrangement for ingenol analogs[5,6]

2. Results and Discussion

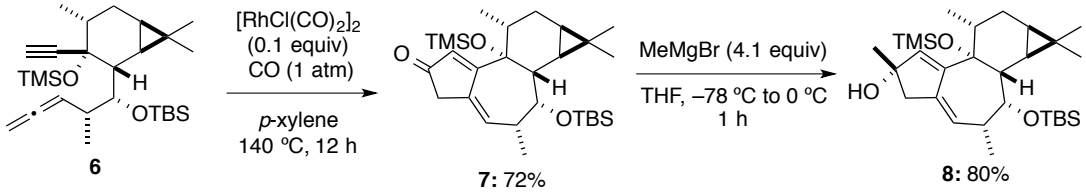
2-1. Synthsis substrate for Pauson-Khand cyclization



Scheme 2. Cyclase phase procedure

- **2** to **3** (chlorination and ozonolysis): Chlorination proceeded stereoselectively due to the steric hindrance of dimethyl cyclopropyl ring.
- **3** to **4** (reductive alkylation and aldol reaction): Alkylated intermediate was too unstable to isolate, therefore one-pot procedure was selected.
- **4** to **5** (nucleophilic addition): Due to steric hindrance of alkyl groups, the reaction proceeded stereoselectively (10:1).

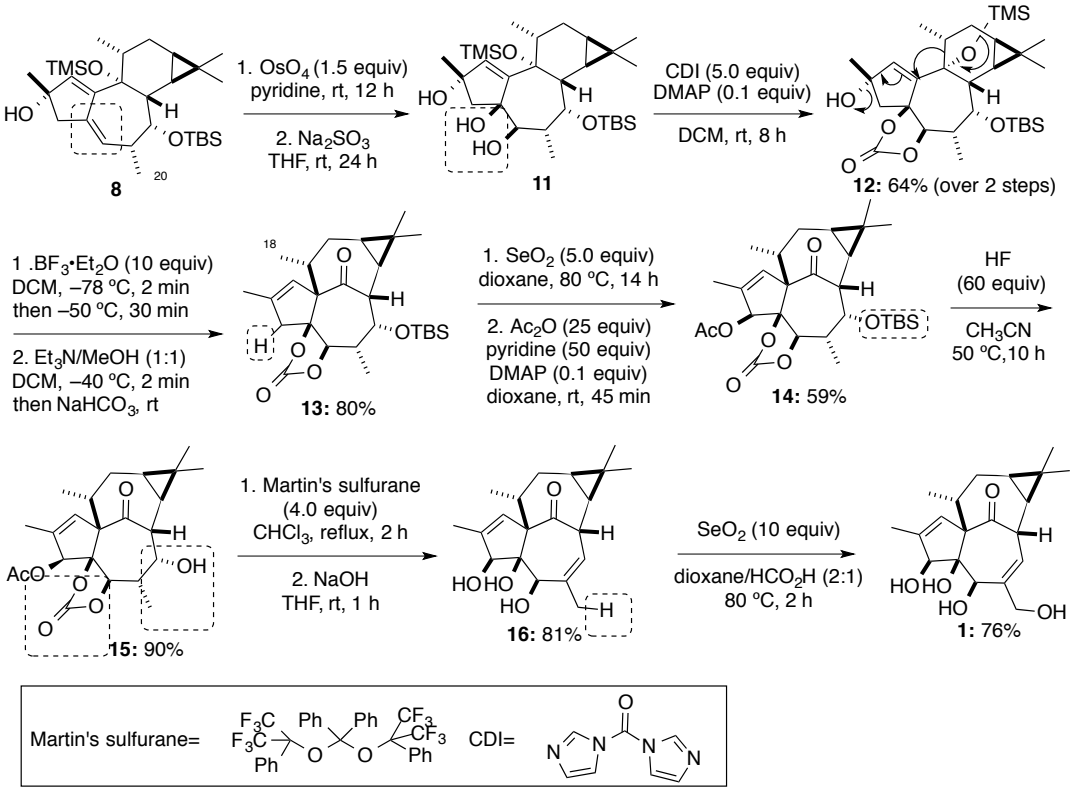
2-2. Key cyclization process



Scheme 3. Synthesis of key intermediate **8**

- **6** to **7** (Pauson-Khand reaction): By using Pauson-Khand reaction,[6] effective ring formation was achieved.
- **7** to **8** (nucleophilic addition): Due to steric hindrance of TMS group, the reaction was proceeded stereoselectively.

2-3. Oxidase phase



Scheme 4. Oxidase phase procedure

- **8** to **11** (dihydroxylation): Oxidation by stoichiometric amount of OsO_4 promoted dihydroxylation chemoselectively due to TMS group and steroselectively due to C-20 methyl group.
- **12** to **13** (pinacol rearrangement): Crucial low temperature and steric hindrance among TMS, TBS, and tight fused rings compare to broad huge ring system eventually enable to set the strained "in, out" stereochemistry.
- **13** to **14** (allylic oxidation): Due to steric hindrance of C-18 methyl group, SeO_2 lead to allylic oxidation steroselectively.
- **14** to **16** (alcohol elimination and global deprotection): Alcohol elimination with Martin's sulfurane and basic hydrolysis with NaOH were smoothly achieved.
- **16** to **1** (allylic oxidation): Final installation of OH group was accomplished by using SeO_2.

3. Conclusion

- The authors achieved the total synthesis of ingenol in 14 steps and 1.2% overall yield through vinylogous pinacol rearrangement.
- This yield compares favorably with natural isolation yield of ingenol or ingenol mebutate [Picato].
- This is good examples that total chemical synthesis holds promise as the best method to prepare and develop terpenoid drug molecules because of both yield and key intermediate **8** as point of divergence for the analogs.

4. References

1. E. Hecker, *Cancer Res*. **1968**, *28*, 2338
2. J. Hohmann, F. Evanics, L. Berta, T. Bartok, *Plata Med*. **2000**, *66*, 291
3. K. Chen, P. S. Baran, *Nature* **2009**, *459*, 824
4. G. Appendino *et al*, *J. Org. Chem*. **1999**, *12*, 3413
5. O. L. Epstein, J. K. Cha, *Angew. Chem. Int. Ed*. **2004**, *44*, 121
6. K. M. Brummond *et al, Org. Lett*. **2002**, *4*, 1931