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

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Science 2013, 341, 878-882.

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).
- 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 largely 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
⇒ 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 reverse reaction is thermodynamically stable.
  ⇒ overcome to this problem, previously strain epoxide structure enable this rearrangement (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).

2. Results and Discussion

2-1. Synthesis substrate for Pauson-Khand cyclization

**Figure 3. Retrosynthetic analysis of ingenol analogs.**

**Scheme 1. Pinacol rearrangement for ingenol analogs.**

**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, 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