Stereoselective Total Synthesis of Hainanolidol and Harringtonolide via Oxidopyrylium-Based [5 + 2] Cycloaddition


1. Introduction

1.1 Harringtonolide and Hainanolidol

• Representative Cephalotaxus nortiterpenes
  ⇒ fused tetracyclic carbon framework
  tropone ring D, bridged lactone (+ THF ring)
• Harringtonolide 1: first isolated from C. harringtonia in 1978
• Hainanolidol 2: isolated from C. haiananensis in 1979
  ⇒ 1: antineoplastic and antiviral active
  2: inactive
  ⇒ THF ring is important?
• Harringtonolide 1: selective anticancer activity

1.2 Previous Work

• The first synthesis of hainanolidol 2 was realized by Mander’s group in 1998
  ⇒ Extremely low yield due to stereoisomerization
• Biomimetic transformation from 2 to 1 by Pb(OAc)₄-mediated transannular oxidation reported.
  ⇒ Validated only by IR and MS

1.3 Author’s motivation

• Confirmation the biomimetic transformation reaction
• Evaluation of the therapeutic potential of 1 and related natural products

1.4 Strategy

• Tropone
  ⇒ Cleavage of ether bridge
• Fused tetracyclic carbon framework
• Oxidopyrylium-based [5+2] cycloaddition
• Decalin moiety
  ⇒ Stereoselective installation of functional groups
  Oxidative ring expansion of furan

2. Result and Discussion

First, decaline derivative with six contiguous stereogenic centers prepared.

Scheme 2. Preparation of a Decalin Derivative with Six Contiguous Stereogenic Centers

Starting material: commercially available ethyl 2-oxocyclohexanecarboxylate (15300 yen/25 g @ Aldrich)

• 10 → 9: Robinson annulation
• 9 → 13b: oxidation and reduction process to obtain desired triol 13b
• 15 → 16: Claisen rearrangement
• 19 → 20: [3,3]-Sigmatropic rearrangement
• 20 → 21: Weinreb ketone synthesis
• 21 → 22: VO(acac)₂-catalyzed oxidative ring expansion
Then, tetracyclic carbon framework was formed via [5+2] cycloaddition.

Scheme 3. [5 + 2] Cycloaddition and Attempts for the Synthesis of Tropone by Dehydration

- 22 → 23: [5+2] cycloaddition (Scheme 4)

Scheme 4. Mechanism of [5+2] cycloaddition

- 23 → 24: lactone formation
- 25 → 2: Direct dehydration process could not be achieved.

⇒ Author developed two-step protocol to open the ether bridge (Scheme 5)

Scheme 5. Opening of Ether Bridge

- 24 → 26: Installation of phenylthio group through a Lewis acid-mediated S_N1' substitution
- 26 → 27: Deprotonation of α-position of phenyl sulfide by LDA and cleavage of ether bridge

⇒ There were two possibilities (27a, 27b), but HSQC spectra indicated that only diene 27a was formed by the cleavage of the C(5)-O bond because of resonance of allyl anion.

Finally, Tropone was formed and desired product was obtained.

Scheme 6. Formation of Tropone and Completion of the Synthesis of 1 and 2

- 27a → 28: Removal of PhS via oxidation by MMPP to convert sulfoxide and reduction with Sml₂
- 28 → 29: [4+2] cycloaddition of diene 28 with singlet oxygen
- 29 → 30: Kornblum–DeLaMare rearrangement
- 30 → 2: Double elimination of water to prepare tropones in 2 and 1
- 2 → 1: Pb(OAc)₄-mediated transannular oxidation

1 and 2 were confirmed by ³¹H and ¹³C NMR of reported natural product.

⇒ The biomimetic transformation from 2 to 1 was confirmed by total synthesis for the first time

3. Conclusion
- The total synthesis of hainanolide and harringtonolide were realized.
- Developed new synthetic route offers the flexibility to access other members of Cephalotaxus norditerpenes and its analogues.
- The biomimetic transformation from hainanolide to harringtonolide was confirmed for the first time.

4. Reference