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

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1. Introduction

1.1 Harringtonolide and Hainanolidol

•Representative *Cephalotaxus* norditerpenes

⇒fused tetracyclic carbon framework

tropone ring D, bridged lactone (+ THF ring)

•Harringtonolide **1**: first isolated from *C.harringtonia* in 1978[1]

• Hainanolidol **2**: isolated from *C. haiananensis* in 1979[2]

⇒**1**: antineoplastic and antiviral active

2: inactive

⇒THF ring is important?

•Harringtonolide **1**: selective anticancer activity[3]

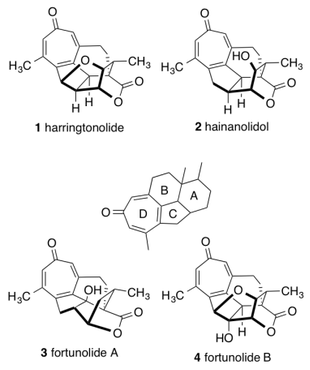


Figure 1. Representative *Cephalotaxus* Norditerpenes

1.2 Previous Work

• The first synthesis of hainanolidol **2** was realized by Mander's group in 1998[4]

⇒Extremely low yield due to stereoisomerization

• Biomimetic transformation from **2** to **1** by $Pb(OAc)_4$-mediated transannular oxidation reported.[5]

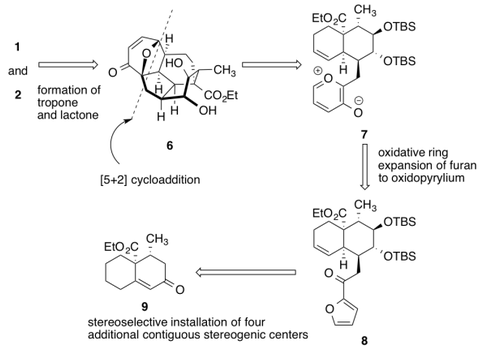
⇒Validated only by IR and MS

1.3 Author's motivation

• Confirmation the biomimetic transformation reaction

• Evaluation of the therapeutic potential of **1** and related natural products

Scheme 1. Retrosynthetic Analysis of **1** and **2**



1.4 Strategy

• Tropone

⇒Cleavage of ether bridge

•Fused tetracyclic carbon framework

⇒Oxidopyrylium-based [5+2] cycloaddition

•Decalin moiety

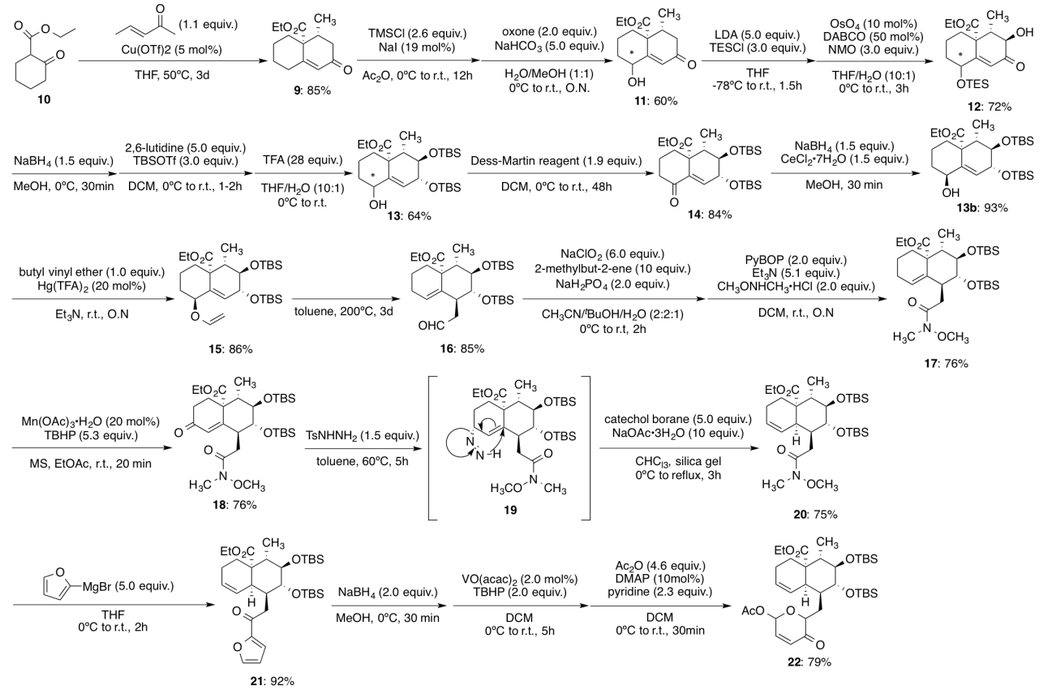
⇒Stereoselective installation of functional groups

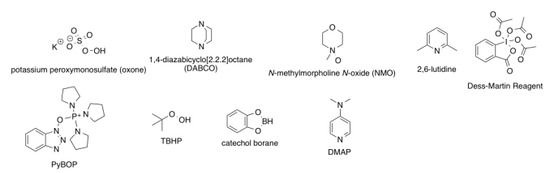
Oxidative ring expansion of furan

2. Result and Discussion

First, decaline derivative with six contiguous stereogenic centers preparated.

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





* (α/β)= 4:1

•Starting material: commercially available ethyl 2-oxocyclohexanecarboxylate (13500 yen/25 g @Aldrich)

•**10**→**9**: Robinson annulation

•**9**→**13b**: oxidation and reduction process to obtain desired triol **13b**

•**15**→**16**: Claisen rearrangement

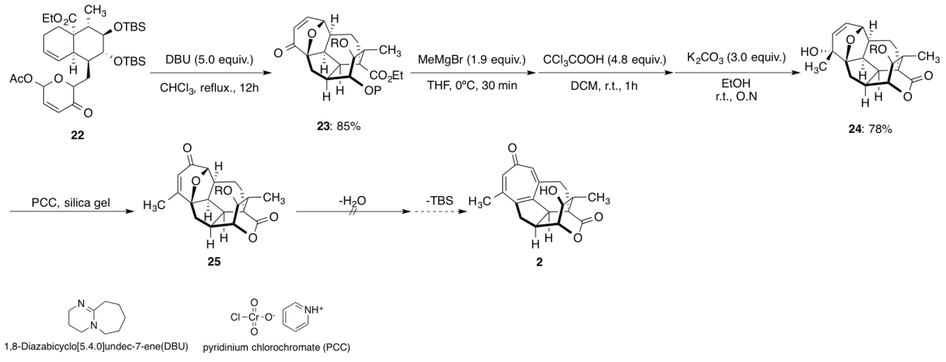
•**19**→**20**: [3,3]-Sigmatropic rearrangement

•**20**→**21**: Weinreb ketone synthesis

•**21**→**22**: $VO(acac)_2$-catalyzed oxidative ring expansion

Then, tetracyclic carbon framework was formed via [5+2] cycloaddition.

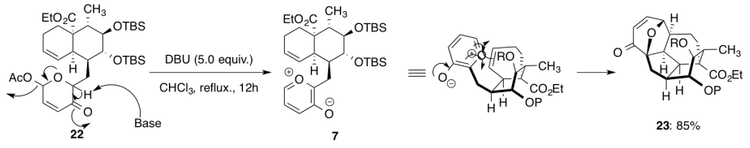
Scheme 3. [5 + 2] Cycloadditon and Attempts for the Synthesis of Tropone by Dehydration



(R = TBS)

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

Scheme 4. Mechanism of [5+2] cycoaddition

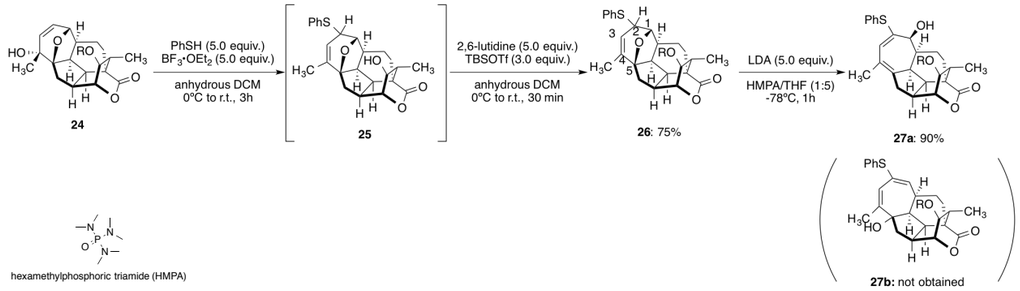


•**23→24**: lactone formation

•**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



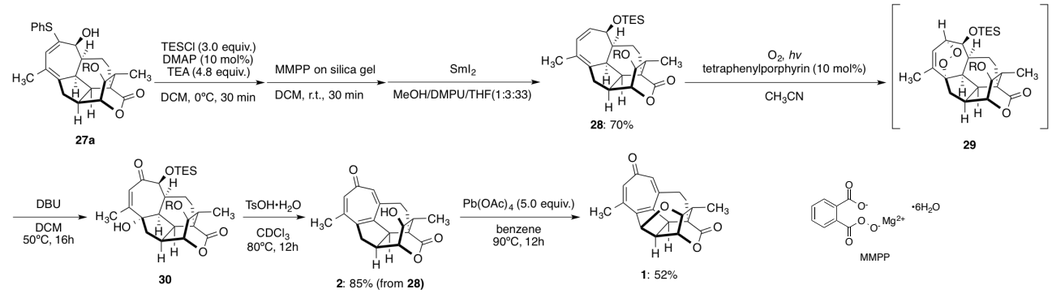
• **24→26**:Installation of phenylthio group through a Lewis acid-mediated S_N1' substitution

•**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 SmI_2

•**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 ^1H and ^{13}C 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 hainanolidol and harringtonolide were realized.

•Developed new synthetic route offters the flexibility to access other members of *Cephalotaxus* norditerpenes and its analogues.

•The biomimetric transformation from hainanolidol to harringtonolide was confirmed for the first time.

4. Reference

1. Buta, J. G.; Flippen, J. L.; Lusby, W. R. *J. Org. Chem.* **1978**, 43, 1002.
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3. Evanno, L.; Jossang, A.; Nguyen-Pouplin, J.; Delaroche, D.; Herson, P.; Seuleiman, M.; Bodo, B.; Nay, B. *Planta Med.* **2008**, 74, 870.
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