

# **Literature Report 3**

#### Total Syntheses of Cephalotane-Type Diterpenoids Cephanolides A–D

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Haider, M.; Sennari, G.; Sarpong, R. J. Am. Chem. Soc. 2021, 143, 2710 Qing, Z.; Mao, P.; Wang, T.; Zhai, H. J. Am. Chem. Soc. 2022, 144, 10640

## CV of Prof. Hongbin Zhai (翟宏斌)

#### **Education:**

- **1981-1985** B.S., Peking University
- **1985-1988** M.S., Peking Union Medical College
- **1988-1995** Ph.D., The Ohio State University
- **1996-1997** Postdoc., The Ohio State University
- **1998-2000** Postdoc., University of California, Berkeley
- **2000-2010** Professor, Shanghai Institute of Organic Chemistry
- **2010-2015.07** Professor, Lanzhou University
- **2015.08-Present** Professor, Peking University Shenzhen Graduate School

#### **Research Interests:**

- Total synthesis of natural products
- Synthetic methods development
- Heterocyclic chemistry/medicinal chemistry





#### **2** Total Synthesis of ( $\pm$ )-Cephanolides A–D

**3** Total Synthesis of (-)-Cephanolides A–D



#### Introduction



 ▶ 2017年由岳建民组从Cephalotaxus sinensis (粗榧)分离得到;
▶ 中国特有树种主要分布在江苏、浙江、安徽、江西、河南、湖南等 地,多生于600-2200米的黄岗岩、砂岩及石灰岩山地;
▶ 粗榧叶、枝、种子、根含有三尖杉酯碱和高三尖杉酯碱等20多种 生物碱有效成分,对治疗白血病和淋巴肉瘤等有一定的疗效。

#### **Proposed Biogenetic Pathways for Diterpenoids**



#### **Reported Total Syntheses of Benzenoid Cephanolides**



#### **Retrosynthetic Analysis**



#### **Synthesis of 19**



#### **Late-stage Oxidation 19**



#### Synthesis of ( $\pm$ )-Cephanolides B and C



#### Synthesis of ( $\pm$ )-Cephanolide D



### Synthesis of ( $\pm$ )-Cephanolide A



#### **Total Synthesis of (±)-Cephanolides A-D**



#### **Reported Total Syntheses of Benzenoid Cephanolides**



#### **Palladium-Catalyzed Cascade Carbopalladation**



#### **Retrosynthetic Analysis**



#### **Synthesis of 30**



#### Investigation of the Pd-Catalyzed Tandem Cyclization



	Entry	29	Reaction conditions	Yield
	1	29a	Pd(OAc) <sub>2</sub> , PPh <sub>3</sub> , Ag <sub>2</sub> CO <sub>3</sub> , MeCN, 120 °C	trace
CO <sub>2</sub> Me	2	29b	Pd(OAc) <sub>2</sub> , PPh <sub>3</sub> , CuI, Et <sub>3</sub> N, MeCN, reflux	ND
он	3	29c	Pd(PPh <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub> , PhMe, reflux; DDQ, DCM, rt	trace
Sn <sup>n</sup> Bu <sub>3</sub>	4	29d	Pd(PPh <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub> , Et <sub>3</sub> N, MeCN, 100 °C	ND
	5	29e	Pd(PPh <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub> , Et <sub>3</sub> N, MeCN, 100 °C	60%
──CO <sub>2</sub> Me	6	29e	Pd(PPh <sub>3</sub> ) <sub>4</sub> , Et <sub>3</sub> N, MeCN, 100 °C	52%
<u> </u>	7	29e	Pd(PPh <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub> , Et <sub>3</sub> N, DMF, 100 °C	71%
	8	29e	Pd(PPh <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub> , Et <sub>3</sub> N, DMF, 120 °C	68%
	9	29e	Pd(PPh <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub> , Et <sub>3</sub> N, DMF, 80 °C	59%

29a

29b

29c

29d

29e

#### Synthesis of 42



#### Synthesis of (-)-Cephanolide A



#### Synthesis of (-)-Cephanolides B, C and D



#### Summary



- ✓ (±)-Cephanolides A-D : 8-14 steps, 1.7%-7.3% overall yields
- ✓ Iterative Csp<sup>2-</sup>Csp<sup>3</sup> cross-coupling
- ✓ Intramolecular inverse-demand Diels-Alder cycloaddition
- ✓ (-)-Cephanolides A-D : 11-14 steps, 3.1%-7.2% overall yields
- ✓ Intermolecular Diels-Alder reaction
- ✓ Palladium catalyzed formal bimolecular [2+2+2] cycloaddition
- ✓ Position-selective  $Csp^3$  and  $Csp^2$  C−H oxidation

#### **The First Paragraph**



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Natural products from *Cephalotaxus*, including alkaloids, terpenoids, flavonoids, and miscellaneous compounds, are well-known for their attractive structures and important biological activities, especially those with antitumor activities. One of the alkaloids, homoharringtonine, has been approved by the FDA for the treatment of chronic myeloid leukemia. In the past decades, great efforts were devoted to isolation of new *Cephalotaxus* diterpenoids due to their unique ring systems and promising antitumor activities, and more than 70 cephalotane-type diterpenoids have been reported. Among them, harringtonolide, the first member of the Cephalo*taxus* troponoids isolated and structurally characterized by Buta et al. in 1978, was shown to inhibit the growth of tobacco and beans and was demonstrated to possess antineoplastic and antiviral activities.

In 2017, cephanolides A-D, four structurally unique cephalotane-type diterpenoids, were isolated from Cephalotaxus sinensis by Yue and coworkers. While cephanolides A-C are A-ring-contracted cephalotane-type C18 dinorditerpenoids, cephanolide D is an A-ring-contracted norditerpenoid. These four natural products represent all the congeners of the benzenoid cephalotane-type diterpenoids discovered to date, which were believed to be biosynthetically derived from the antitumor *Cephalotaxus* troponoids. It was proposed that electrocyclic annulation of the tropone moiety within a cephalotane troponoid, e.g., fortunolide A, generates a cyclopropanone-containing intermediate, subsequently undergoing Baeyer–Villiger-type oxidation and hydrolysis to afford the benzenoid motif.

The distinctive structural features and significant biological activities of cephalotane-type diterpenoids have aroused broad interest from the synthetic community. Since Mander and co-workers reported the formal synthesis of  $(\pm)$ -harringtonolide for the first time in 1998, a number of synthetic studies toward total synthesis of the natural products of this family have been documented. Herein, we report the asymmetric and divergent total syntheses of cephanolides A-D featuring a Pd-catalyzed formal bimolecular [2+2+2] cycloaddition reaction via a partially intermolecular cascade reaction sequence involving multiple carbometalations to rapidly assemble the key tetracyclic backbone.





We have developed an efficient divergent strategy for the asymmetric total syntheses of cephanolides A–D in 11–14 steps from known chiral alcohol. The striking features of the current syntheses include (i) a substrate controled diastereoselective intermolecular Diels-Alder reaction to form the highly functionalized 6-6 cis-fused rings, (ii) a palladium-catalyzed formal bimolecular [2+2+2] cycloaddition reaction via a partially intermolecular cascade reaction sequence involving multiple carbometalations to rapidly install the key tetracyclic skeleton, and (iii) the late-stage oxidative diversification through position-selective sp3 (benzylic) and sp2 (on the benzene ring) C-H oxidation, enabling divergent assembly of the four natural products. The present work may facilitate larger-scale preparation and further biological studies of various cephalotane-type diterpenoids.

1. We have found that chemical network analysis, which is rooted in seminal reports from Corey, provides an expedient guideline for identifying the strategically most important bonds for this purpose. (权宜之计)

2. However, the asymmetric total syntheses of cephanolides C and D have not been disclosed hitherto.(迄今为止)

 Our synthesis plan sets the stage for the preparation of other structurally complex Cephalotaxus norditerpenoids that involve scaffold modifications.( 为…的准备奠定了基础)

# Thanks for your attention