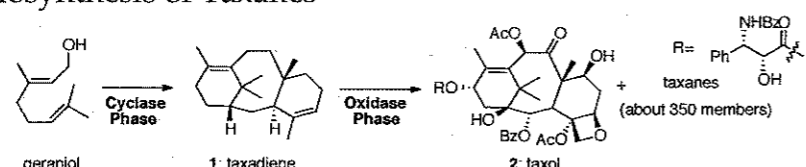


**Scalable enantioselective total synthesis of taxanes.**Mendoza, A.; Ishihara, Y.; Baran, P. S.  
Nature Chemistry, 2012, 4, 21–25.**1. Introduction****1.1 Two big issues in total synthesis**

- Large-scale synthesis of biologically important compounds.
- Diversity-orientated synthesis of natural product families.

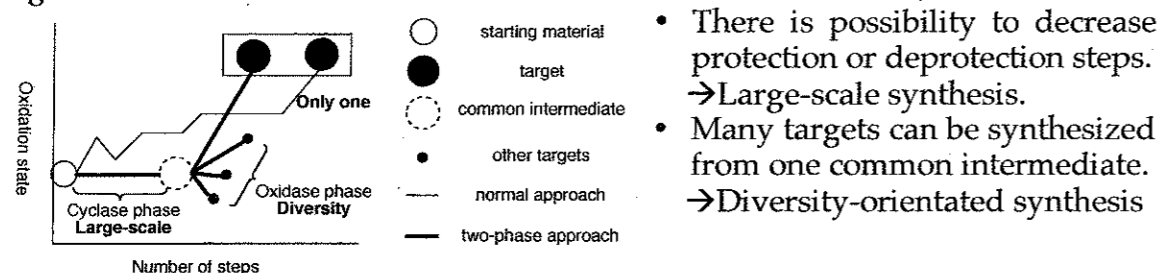
**1.2 Two-phase approach**

- Authors indicated that one of the solutions is two-phase approach inspired by biosynthesis (Scheme 1).

**Scheme 1. Biosynthesis of Taxanes**

Cyclase phase; Construction of framework of taxanes  
Oxidase phase; Chemo- stereo- and regioselective oxidation

- If this method is applied to total synthesis, there are two merits (Figure 1).

**Figure 1.**

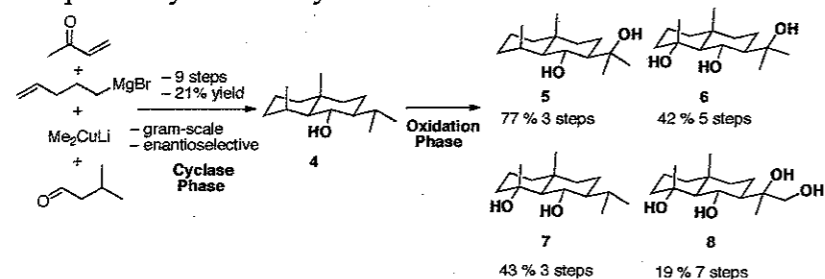
- There is possibility to decrease protection or deprotection steps.  
→ Large-scale synthesis.
- Many targets can be synthesized from one common intermediate.  
→ Diversity-orientated synthesis

**Challenges for using two-phase approach**

- Chemo-, stereo-, and regioselective C–H oxidation is difficult.
- Large-scale synthesis of skeleton of natural product is unknown.

**1.3 Previous work of authors**

- They demonstrated two-phase approach. (Scheme 2).

**Scheme 2. Two-phase synthesis by site-selective C–H oxidations<sup>2</sup>**

- Compound 4 can be synthesized in gram-scale (Large scale synthesis).

- Compound 4 is common intermediate for compound 5-8 (Diversity-orientated synthesis).

**What is next target?****1.4 In this work → 'Cyclase phase' for the Taxanes**

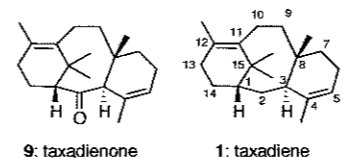
- Taxanes form a large family of terpenes comprising over 350 members.
- The most famous of taxanes is Taxol (2), widely known as an anticancer drug.  
→ These features are suitable to demonstrate two-phase approach.

What compound is suitable for the endpoint in cyclase phase?

→ There are two candidates.

- Taxadiene (1); theoretically reasonable endpoint, compared to biosynthesis.
- Taxadienone (9); practically reasonable endpoint, considering from the facts that selective oxidation from taxadiene is difficult and taxadiene can be synthesized from taxadienone.

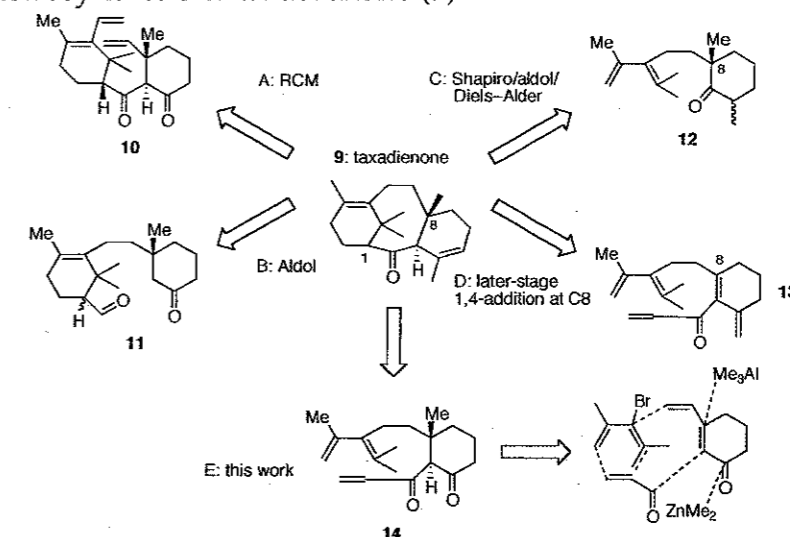
- Total synthesis of taxadiene (1) was only reported by Williams<sup>3</sup> in 26 steps. Total yield was 0.34%. But total synthesis of taxadienone has not been reported.

**Figure 1.**

- In this work, they synthesized taxadienone (9) and taxadiene (1) in gram-scale.
- Key to success for gram-scale synthesis are decreasing steps by three-component coupling and only one enantioselective reaction.

**2. Results and discussion****2.1 Strategy for taxadienone**

- To synthesize taxadienone in gram-scale, they investigated several pathways.

**Scheme 3. Retrosynthesis of taxadienone (9)**

A: Substrate 10 would take many steps to build and require two separate enantioselective reactions.

B: Desired cyclization from compound 11 did not proceed.

C: Substrate **12** required many steps to construct and to control stereocenter at C8 was very challenging.

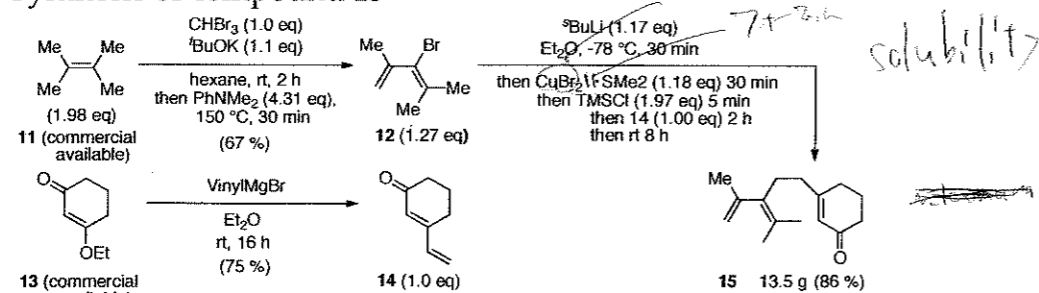
D: This Diels–Alder reaction did not proceed.

E: – Only one enantioselective reaction

– Easy access to compound **14** by three-component coupling

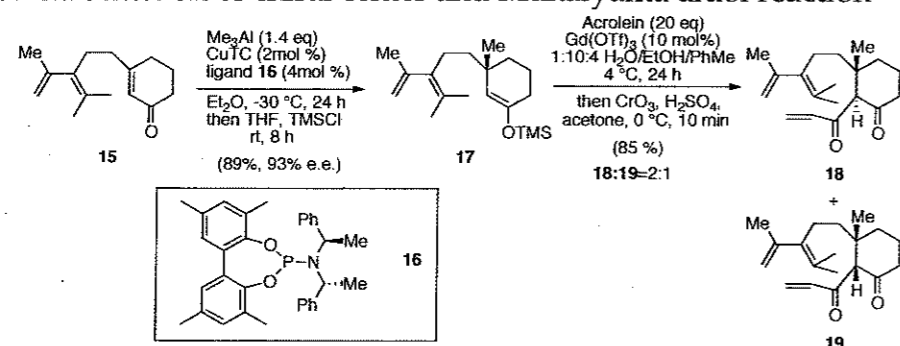
## 2.2 Enantioselective total synthesis of taxadienone (5)

### Scheme 4. Synthesis of compound **15**



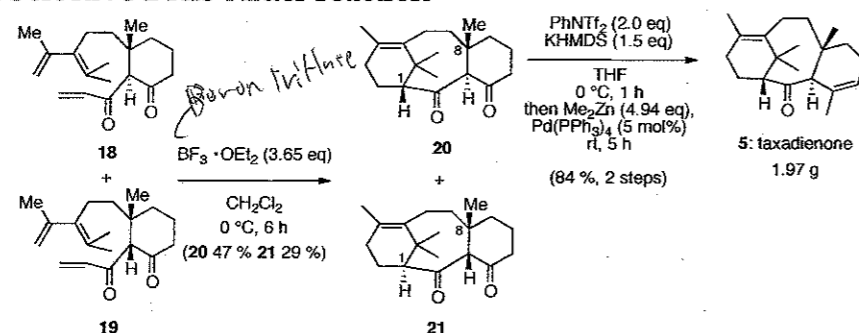
- **12** and **14** → **15**; TMSCl acted as a hard Lewis acid accelerates unusual 1,6-addition.

### Scheme 5. Introduction of chiral center and Mukaiyama aldol reaction



- **15** → **17**; cuprate generated in situ and chiral phosphoramidite ligand **16** is key to afford high yield and enantioselectivity.
- **17** → **18**; they used various kinds of Lewis acid and other catalysts. At last, they found Kobayashi condition<sup>4</sup> with lanthanoid salts generated compound **18**. (dr=2:1)

### Scheme 6. Selective Diels–Alder reaction

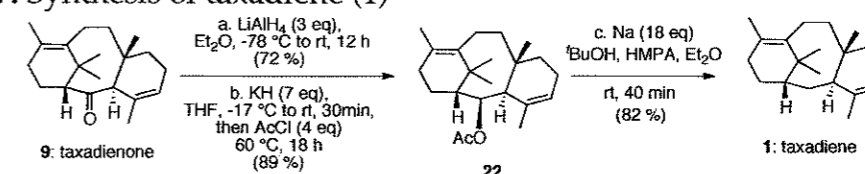


- **18** → **20**; This Diels–Alder reaction had been reported on similar system<sup>3</sup>. Although undesired diastereomer was obtained in 29%, diastereoselectivity at C1 position was almost perfect. (> 99:1)

- **19** → **5**; enol triflate formation followed by Negishi coupling to generate taxadienone (**5**).

## 2.3 Gram-scale synthesis of taxadiene (1)

### Scheme 7. Synthesis of taxadiene (1)



- 1g-scale synthesis of taxadiene (**1**) is achieved through 3 steps from **9**.

## 3. Conclusions

- Enantioselective gram-scale synthesis of taxadienone (**9**) and taxadiene (**1**) is achieved only 7 steps in 20% and 10 steps in 11% (previous yield is only 0.34%) as the endpoint in cyclase phase.

## 4. Perspective

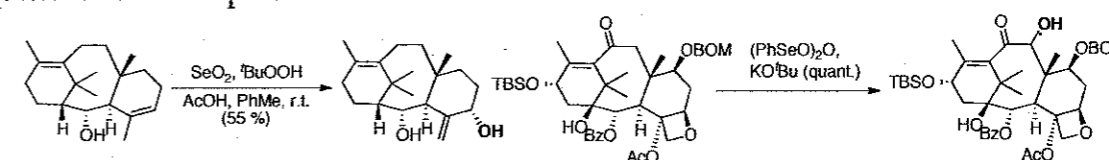
### 4.1 Cyclase phase

- Problem in this paper; only the 2:1 diastereoselectivity in the aldol reaction
- Plausible solution; to optimize the amount of acrolein and reaction condition with various additives

### 4.2 Oxidase phase

- They envision trying various kinds of known or unknown oxidation reaction (Scheme 8).

### Scheme 8. Examples of known oxidative transformations in taxanes



## 5. Reference

1. Ishihara, Y.; Baran, P. S. *Synlett*, **2010**, *12*, 1733.
2. Chen, K.; Baran, P. S. *Nature*, **2009**, *459*, 824.
3. Rubenstein, S. M.; Williams, R. M. *J. Org. Chem.*, **1995**, *60*, 7215.
4. Kobayashi, S.; Hachiya, I.; Yamanoi, Y. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 2342

**Abbreviations** Bz, benzoyl; Ac, acetyl; TMSCl, trimethylsilyl chloride; CuTC, copper(I) thiophene-2-carboxylate; PhNTf<sub>2</sub>, N-phenylbis(trifluoromethanesulfonyl)amide; KHMDS, potassium hexamethyldisilazide; Pd(PPh<sub>3</sub>)<sub>4</sub>, tetrakis(triphenylphosphine)palladium; BOM, benzyloxymethyl; TBS, Tert-butyldimethylsilyl;