# Overviews of Cascade reactions and Multi Component Reactions

**~ These can be the ideal synthetic methodologies??~**

<Contents>



Literature Seminar 2009/1/7

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# 1.Overview ~ cascade reactions

cf.Dr.Kuramochi's lit seminar in 2004

...form several bonds in one sequence without isolating the intermediates, changing the reaction conditions, or adding reagents.

–Tietze. *chem.rev.***1996**, *96*, 115

...include any examples in which the reaction conditions are altered during the process...further reagents are added at various points..however exclude multidirectional reactions in which two or more reactions occur on the same substrate, but essentially in isolation of one another...

–Nicolaou. *ACIE* .**2006**, *45*, 7134

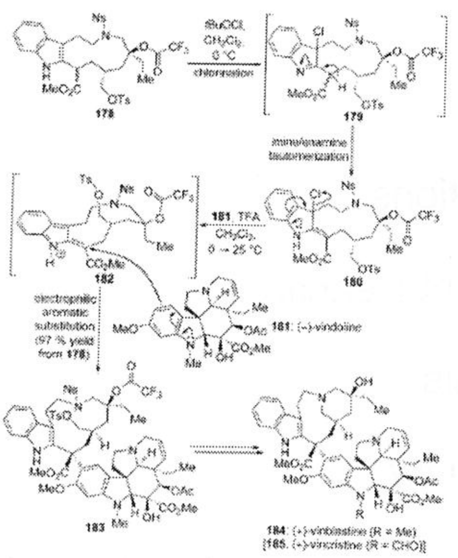
## <Its characters and my impressions>

**1.Intramolecular reaction**

⟶ synthetic approach??

**2.Sometimes exploiting drastic yield, stereoselectivity(diastereo.enantio)**

ex.Fukuyama's total synthesis of (+)-vinblastin



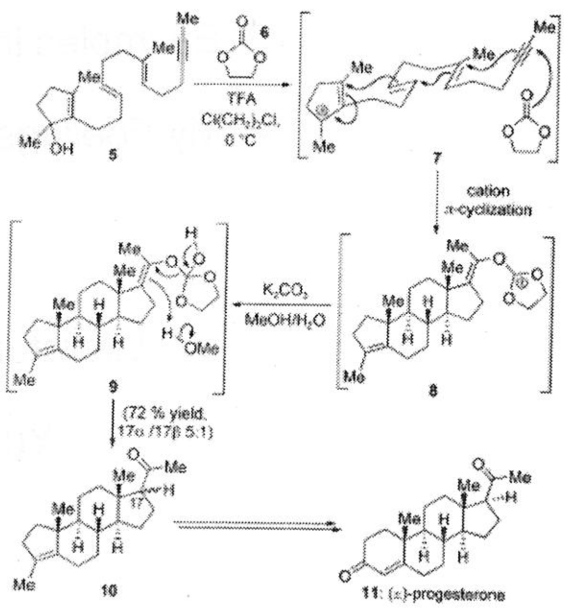
100% requisite stereochemistry
97% overall yield!

↑

Is there general rules ??
Does the fascinating result depend on the substrate??

Fukuyama et al *JACS,* **2002**, 124, 2137

ex.Johnson's total synthesis of progesterone



Johnson et al *JACS,* **1971**, 93, 4332

**3. Biomimeticy**

Without exception, the most complex organic architectures have been produced by natural organisms.

–J.N.Johnston *Chem.Rev.* **2005,** *105*, 4730

### 4. Many examples for total synthesis

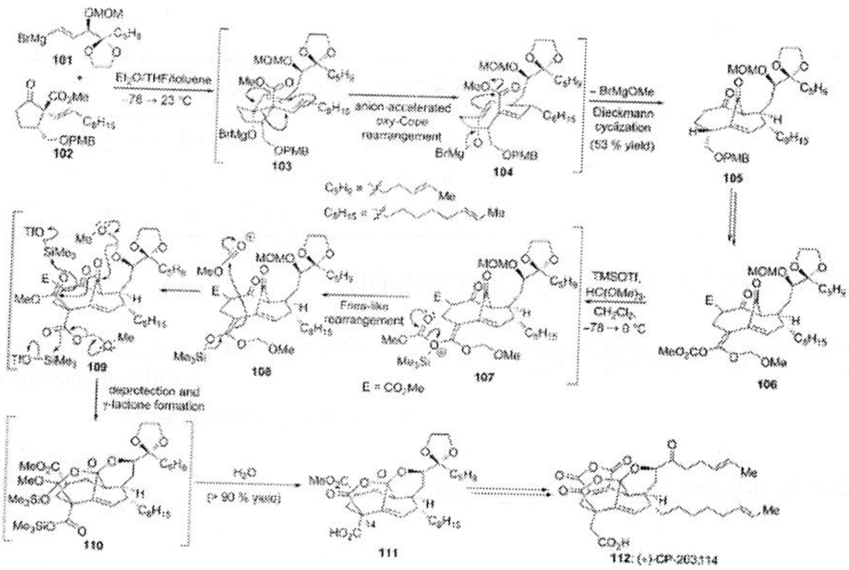
enough to classify the reactlon features. Nicolaou. *ACIE* .**2006**, *45*, 7134

**a. Nucleophilic cascades**
**b. Electrophilic cascades**
**c. Radical cascades**
**d. Pericyclic cascades**
**e. Transition-Metal catalyazed cascades**

### 5. Beautiful synthesis

Art in Science

– Malacria *Chem.Rev.* **1996**, 96, 289




Shair et al *JACS.* **2000**, *122*, 7424

### 6. Efficiency

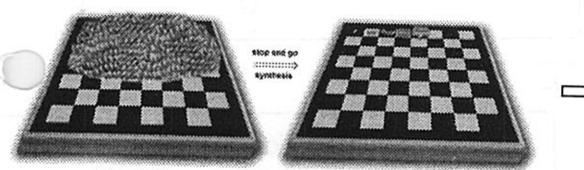
the minimization of...the amounts of solvents, reagents, absorbents, energy, and labour ...would be dramatically decreased.

–Tietze *chem.rev.***1996**, *96*, 115

atom economy, bond economy, step economy...

–Trost *science* **1991**, *254*, 1471 etc

traditional
="stop and go" synthesis ⟶ cascades




MacMillan *synlett*, **2007,** *10*, 1477

cf) Taxol 1ton pharmaceutical demand
= 170000 tons of SM(37 step synthesis)

All admires cascades without any hesitation...

but

Cascades should strongly require

{ **the preparation for appropriate skellton**
**the reaction optimization**

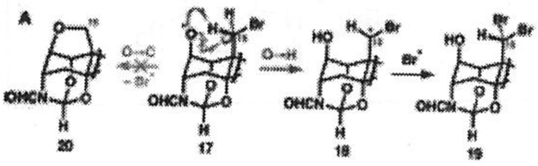
↕

The chance of new reactivity??

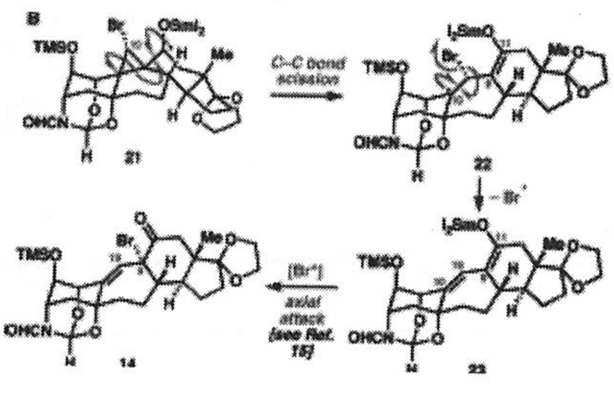
### 7. Adventure for breakthrough-like new reactivity

⟸ I think the most important aspect !!!

ex) Baran's total synthesis of cortistatin A



Baran et al.*JACS*.**2008**, *130*, 7241



# 2. Overview ~Multicomponent reactions(MCR)

Reactions in which more then two starting compounds react to form a product in such a way that the majority of the atoms of the starting compounds can be found in the product ...

– Ugi *ACIE* **2000**, *39*, 3168

Basic types of MCRs

| MCR type | General reaction scheme |
|---|---|
| I | $A+B \rightleftharpoons C \rightleftharpoons \ldots O \rightleftharpoons P$ |
| II | $A+B \rightleftharpoons C \rightleftharpoons D \ldots O \rightarrow P$ |
| III | $A \rightarrow B+C \rightarrow D \rightarrow \ldots O \rightarrow P$ |

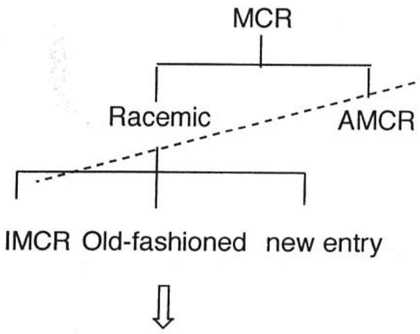
observed in biochemical reaction, but seldom in preparative chemistry

<Its character and my impression>

**1. Intermolecular reactions** → different from cascades in this aspect although quite similar for the "one-pot" like reaction.

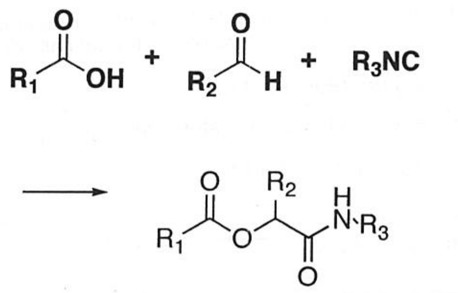
→ reaction character??

**2. Moderate number of reaction manner**

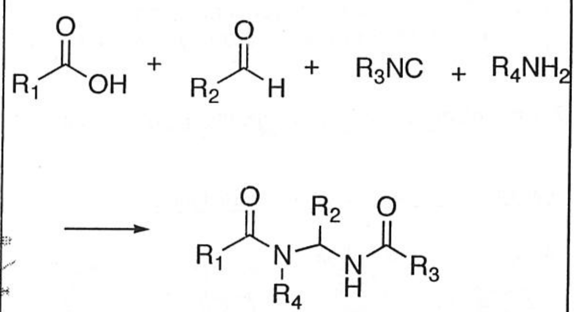


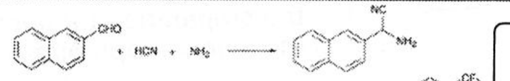
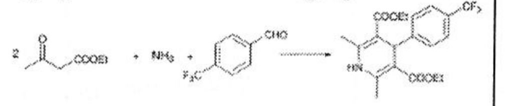
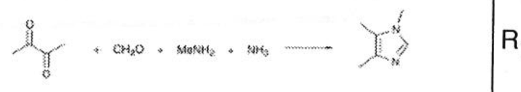
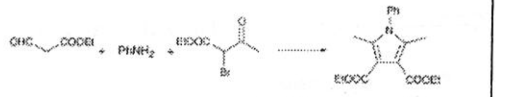
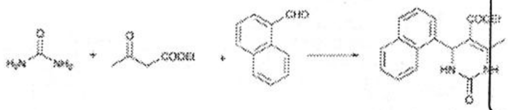
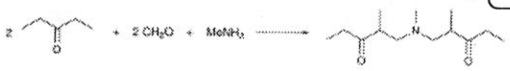
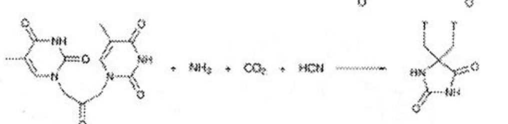

IMCR (Isocyanide MultiComponent Reactions)

Passerini reaction




Ugi reaction



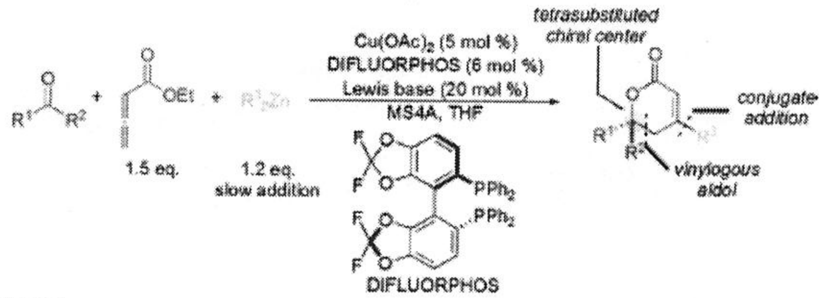

| Name of the reaction | Year of discovery | Example[a] |
|---|---|---|
| Strecker synthesis[18] | (1838) 1850 |  |
| Hantzsch dihydropyridine synthesis[19] | 1882 |  |
| Radziszewski imidazole synthesis[21] | 1882 |  |
| Hantzsch pyrrole synthesis[22] | 1890 |  |
| Biginelli reaction[23, 24] | 1891 |  |
| Mannich reaction[26] | 1912 |  |
| Bucherer–Bergs hydantoin synthesis[28, 29] | 1941 |  |

[a] T = thymine.

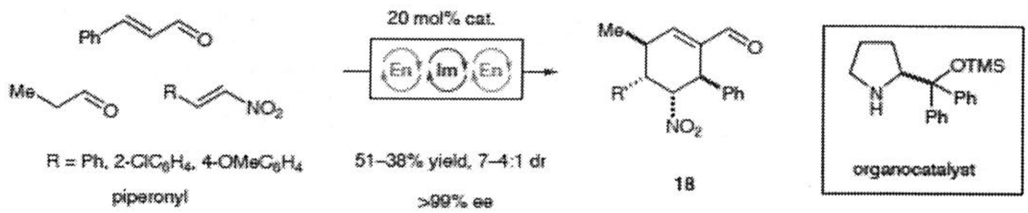
AMCR (Assymmetric MultiComponent Reactions) cf.Mr.Chen's lit seminar in 2006

Cu-Catalyzed AMCR

Shibasaki et al *JACS* **2007**, *129*, 7439




Organo-catalyzed AMCR

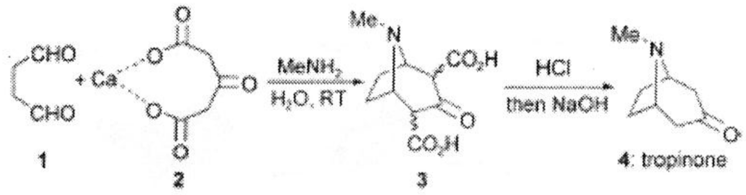



Enders et al. *Nature*. **2006**, *441*, 861

**3. Similarity with cascade reactions**

This Enders' MCR is also expressed "organo-cascade reaction" in another paper.

Robinson's synthesis of tropinpne




Its synthetic route also has cascade-like character.

⇩

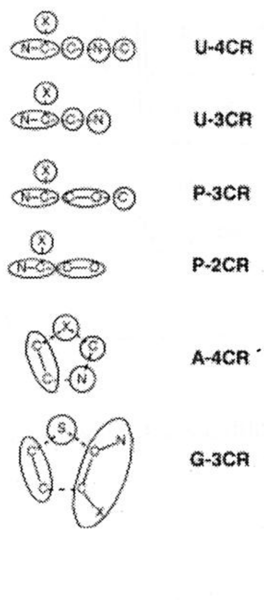
Diffinisions of both should be very fluid. — Of course, cascade reaction can proceed intermolecularly.

**4. Quite a few examples for total synthesis of complex molecules**

→ Due to the limitation of possible skeltons??

→ One of the most attractive exceptions are Fukuyama's Ecteinascidin 743 and Johnson's zaragozic acid C

general possible skeltons

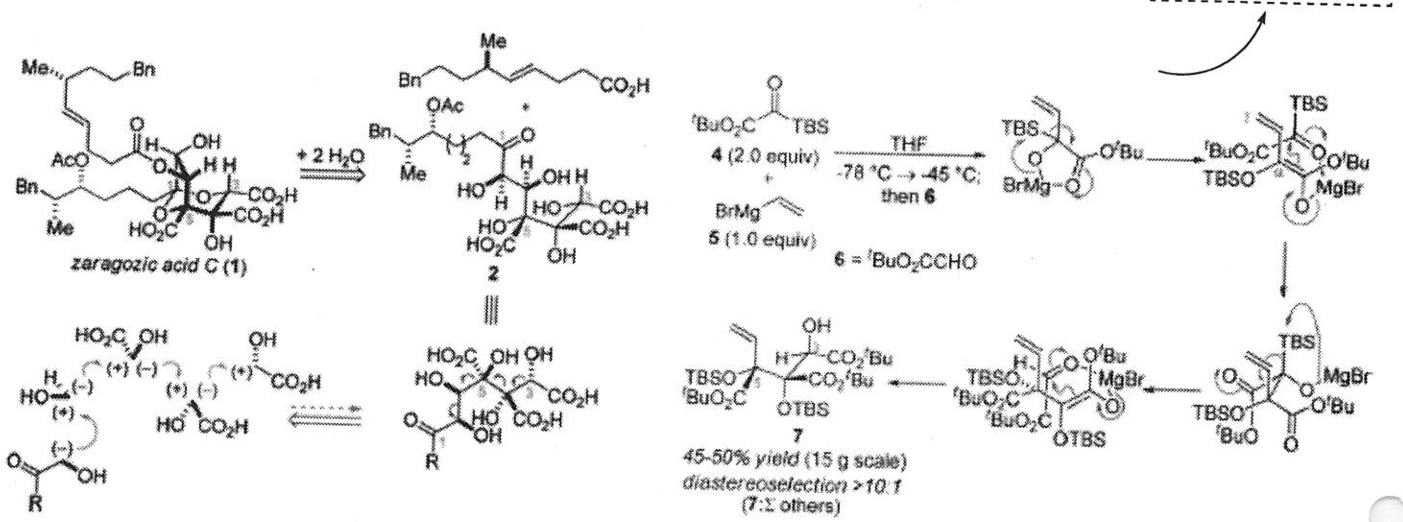



Asinger 4 MCR

Gewald 3 MCR

Johnson's synthesis of zaragozic acid C — Johnson et al. *JACS.* **2008**, *130*, 17281

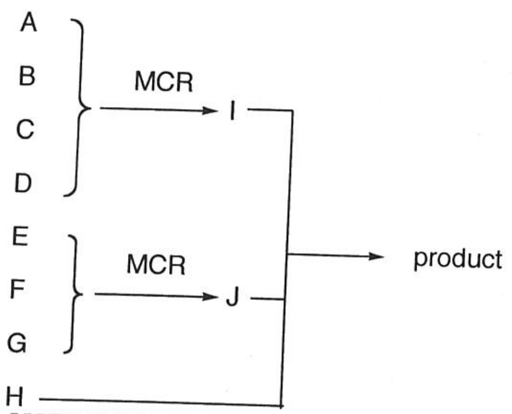
new entry of MCR

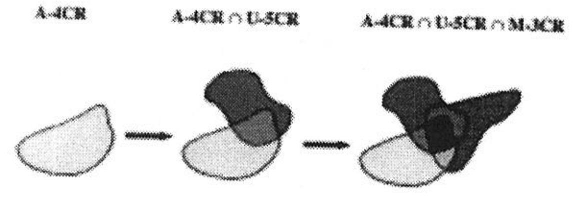



## 5. Efficiency

The multicomponent reactions are responsible for this higher effficiency, not only because of intrinsic aspects of the reaction such as superior atom economy , atom utilization and selectivity, as well as lower level of by-products,but also because of extrinsic aspects of the prossesing reaction, such as simpler procedures and equipment, lower costs, time, and energy, as well as more environmentally friendly criteria.

–Yus *ACIE.* **2005**, 44, 1602




Infinite number of combination of MCRs can occur conceptually, but 7-MCR in real.

...the MCRs already come quite close to the idea of an "ideal synthesis"...

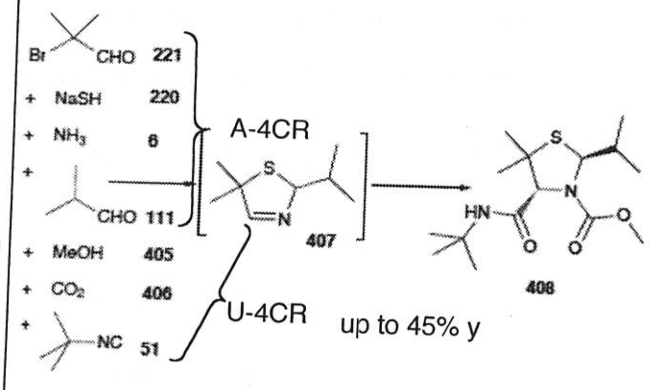
–Ugi *ACIE.* **2000,** 39, 3168

MCRs have the intense possibility to achieve the most convergent "ideal synthesis"....but only in theory??

...possible if the starting materials are well-chosen.

–Ugi *ACIE.* **2000,** 39, 3168

ex)




Ugi et al. *ACIE.* **1993**, 32, 563

I think MCRs never aquire the ability to achieve genaral application due to its specificity (depending on backbone structure of substrates) as well as cascade reactions.

## 6. Its intensive application to DOS(Diversity Oriented Synthesis)

← thought to be the most essential aspect.

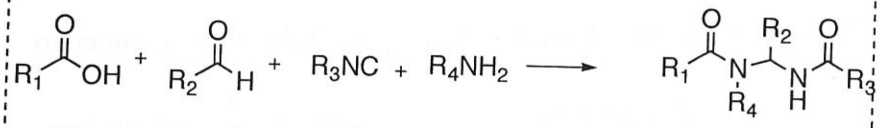
...aimed at a collection of many compounds having structual complexity and diversity.

...to synthesize efficiently a collection of small molecules capable of perturbing any desease-related biological pathways.

—Screiber *science*. **2000**, 287, 1964

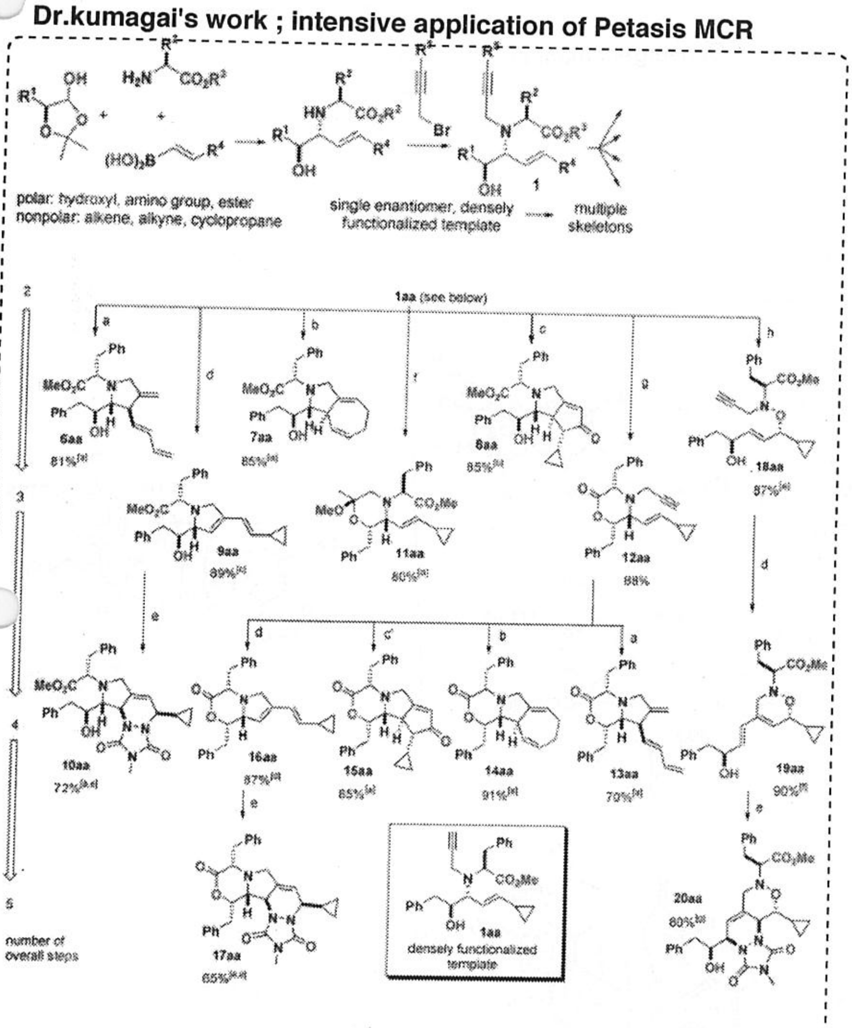
← not only diversity but also molecular structure(complexity, stereochemistry...) seems to be surely crucial.

In Ugi reaction



20 × 20 × 20 × 20 = 160000!!!

**Dr.kumagai's work ; intensive application of Petasis MCR**




Schreiber et al. *ACIE*. **2006**, 45, 3635

It is true that the concept of MCR surely realizes
the multiple(and complex) skeleton synthesis efficiently, but...

**the DOS character "randomness" should cancel out the advantage.**

The fact that there are no DOS-oriented drugs supports my opinion???

**Fascinating example "genetic algorythm"**

**Replication** storing all datas

**Crossover**

ABCD → ABGH
EFGH → EFCD

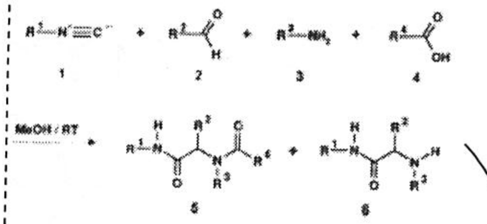
**Mutation**

ABCD → ACBD

Random choice 20

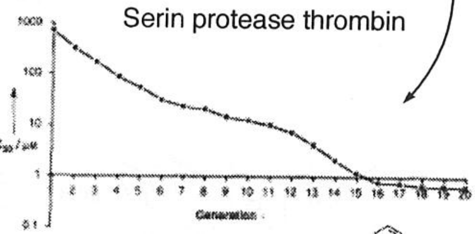
Crossover & Mutation 20

Selection of the most active 20

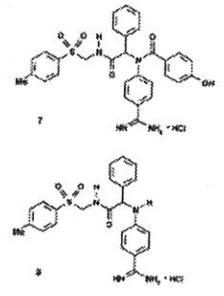


assay

Serin protease thrombin




turned to be the best

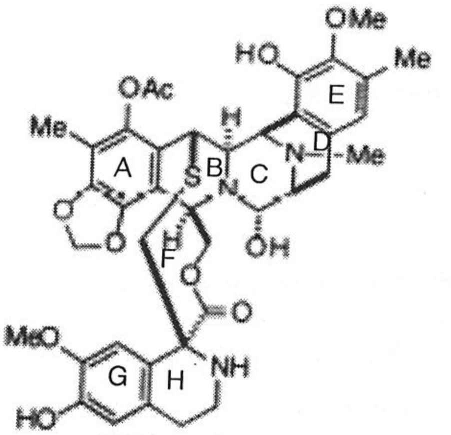


Weber et al. *ACIE*. **1995**, 34, 2280

# 3. Examples in Total synthesis

1. Ecteinascidin 743 ~Cascade vs MCR ~

cf) Mr.Hara's lit seminar in 2006




Ecteinascidin 743 (1)

**Reported total synthesis**

Corey et al. *JACS*. **1996**, *118*, 9202
*OL*. *2000*, *2*, 993(optimized)

→ Cascade Reaction

Fukuyama.et al. *JACS*.**2002**, *124*, 6552

→ MCR(Ugi reaction)

Zhu.et al. *JACS*.**2006**, *128*, 87

→ Convergent manner

*

Classifying the steps in 3 routes

**a. C-C(X) bond forming**

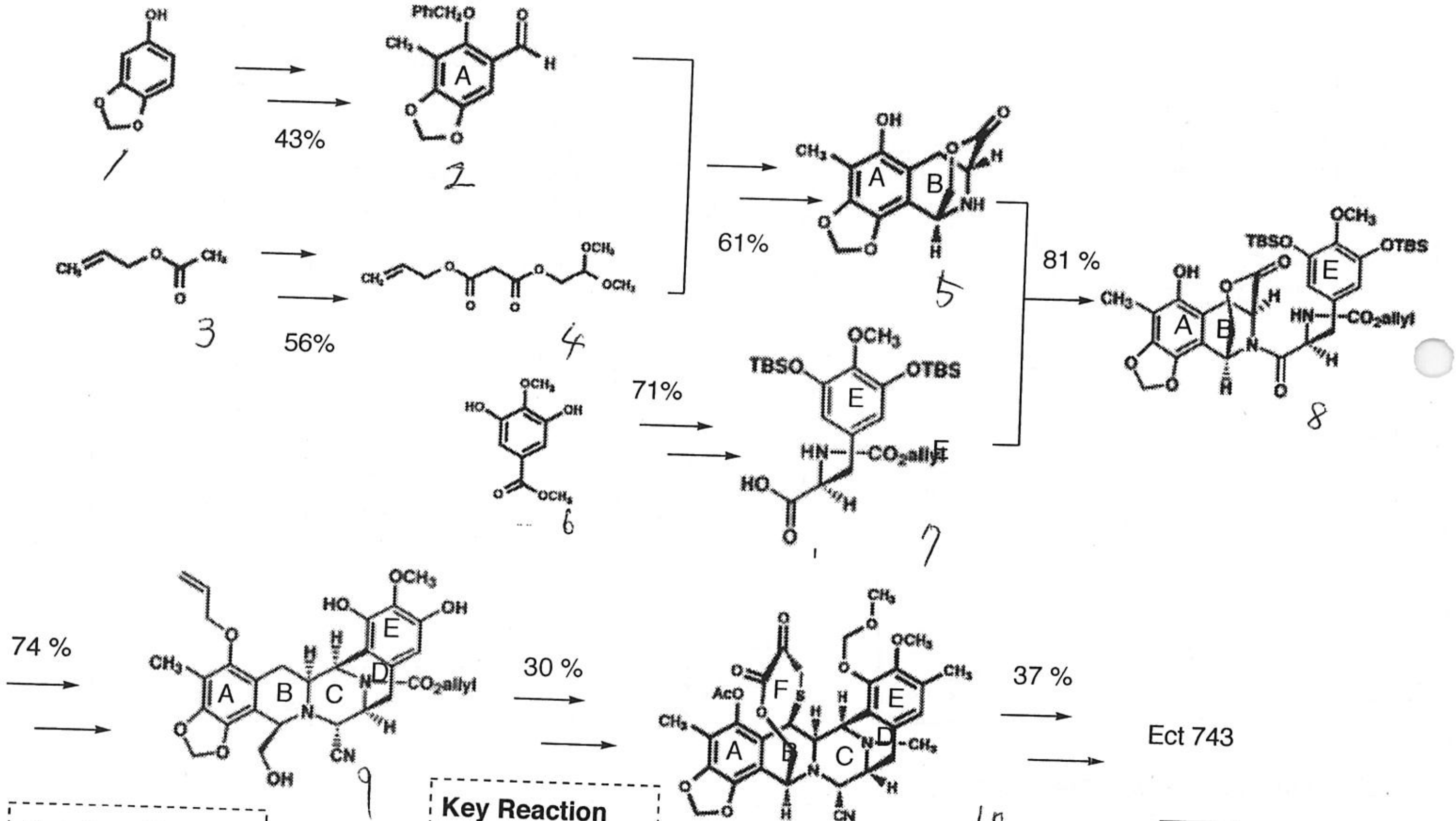
**b. Redox**

**c. Protection/Deprotection**

↓

a should be maximamized.
b,c minimamized.

**Corey et al**




Ect 743

**Key Reaction**

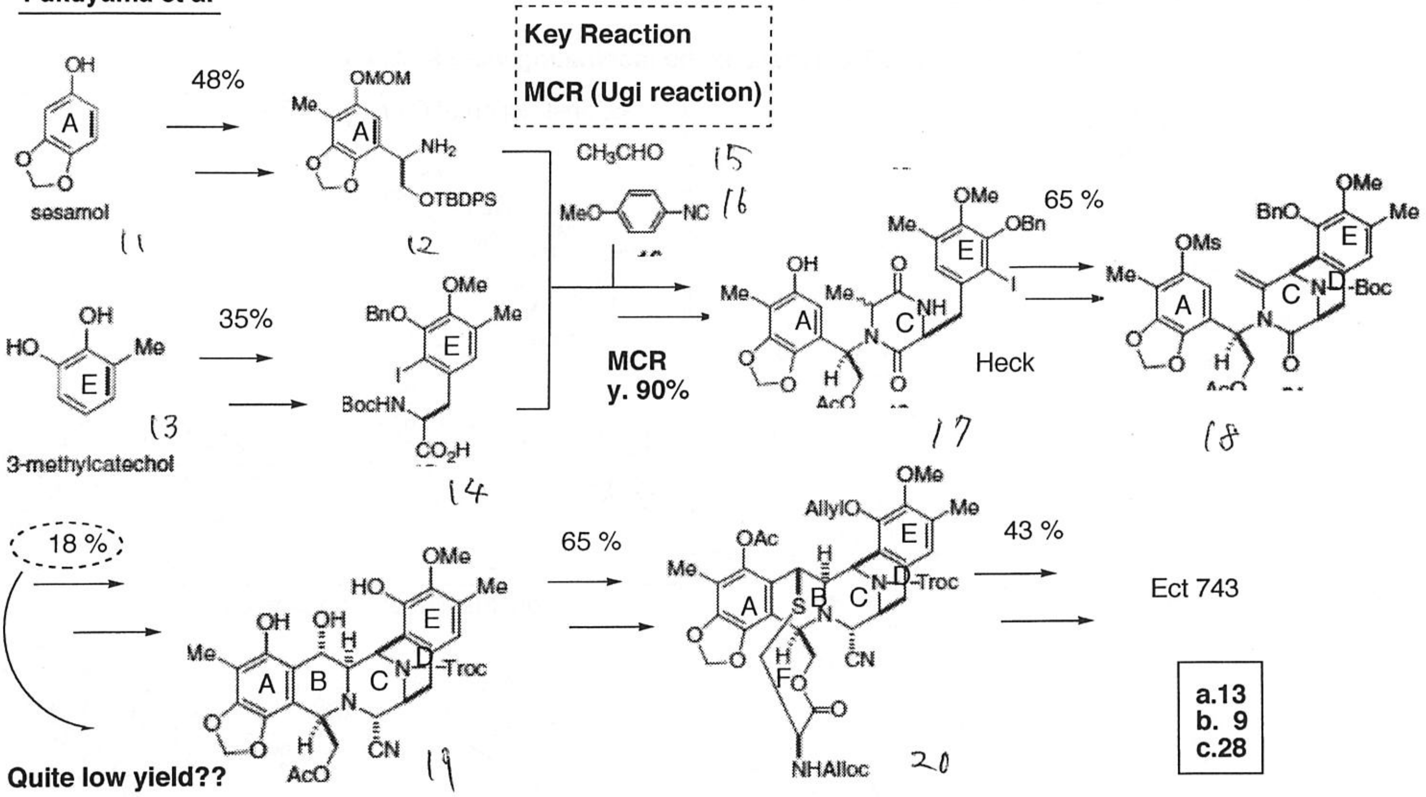
**Cascade Mannich**

**Key Reaction**

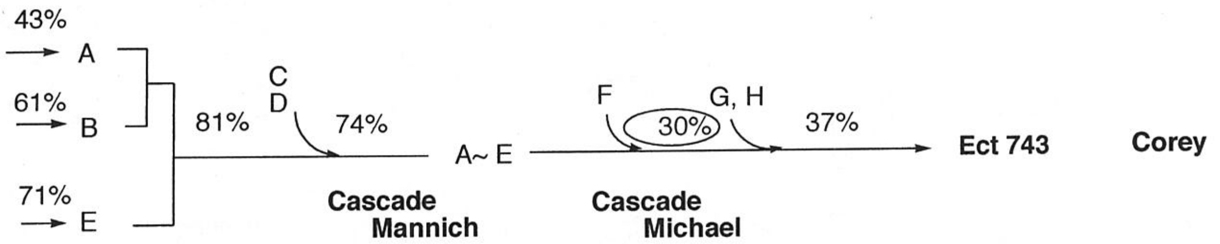
**Cascade Michael**

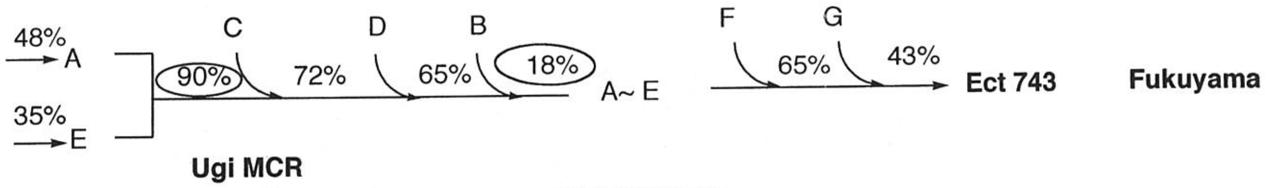
a. 13
b. 3
c. 15

## Fukuyama et al




## Comparison of both tactics (especially for ring construction)



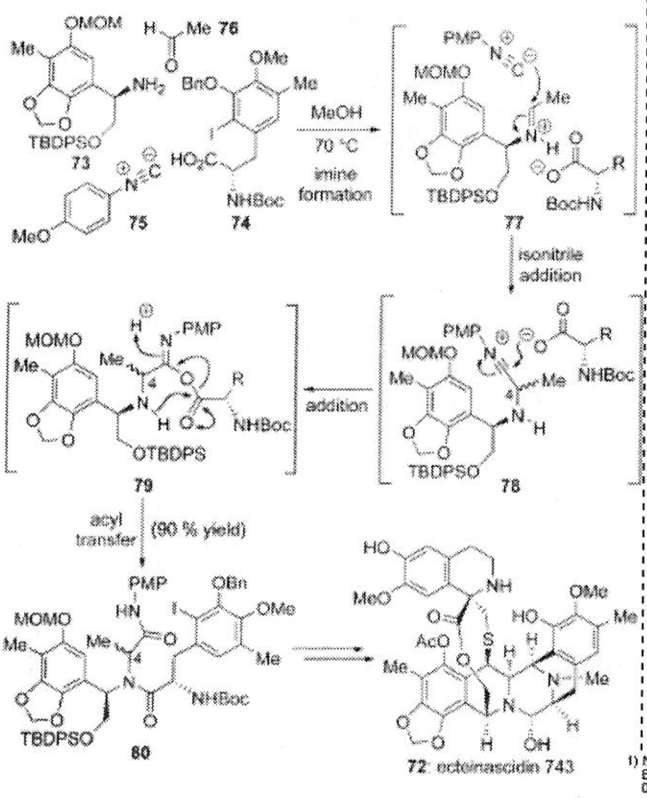




| Routes | Total Steps | Total Yields (%) | A~E (%) | Key (%) | C-X (%) | Protect/Deprotect (%) |
|---|---|---|---|---|---|---|
| **Corey(cascade)** | **34** | **1.7** | **16** | **74, 30** | **38** | **44** |
| **Fukuyama(MCR)** | **50** | **0.8** | **2.7** | **90** | **26** | **56** |

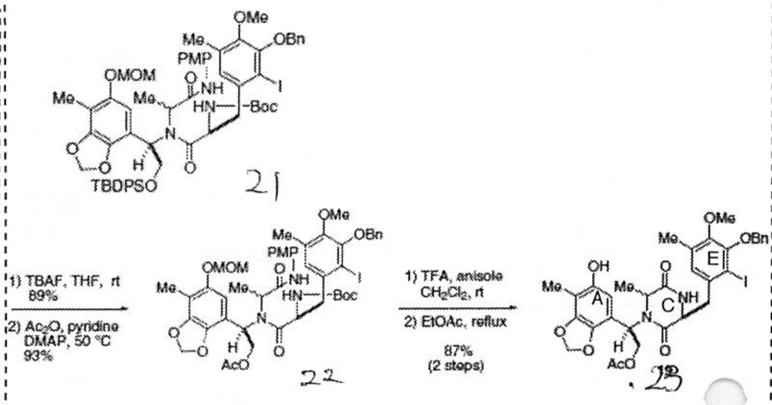
## Comprison of both A~E ring construction

**Fukuyama's route** **Intensive MCR realizes the fascinating yield 90%, but...**

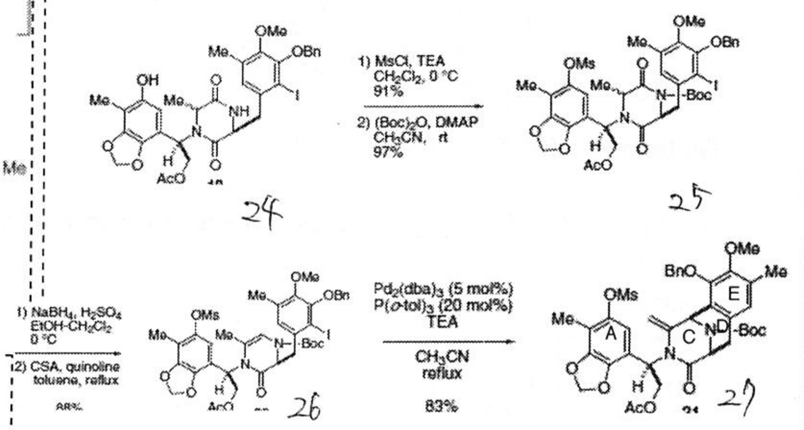
**<Ugi MCR>**
**y. 90%**




<Construction of C ring> y. 72%

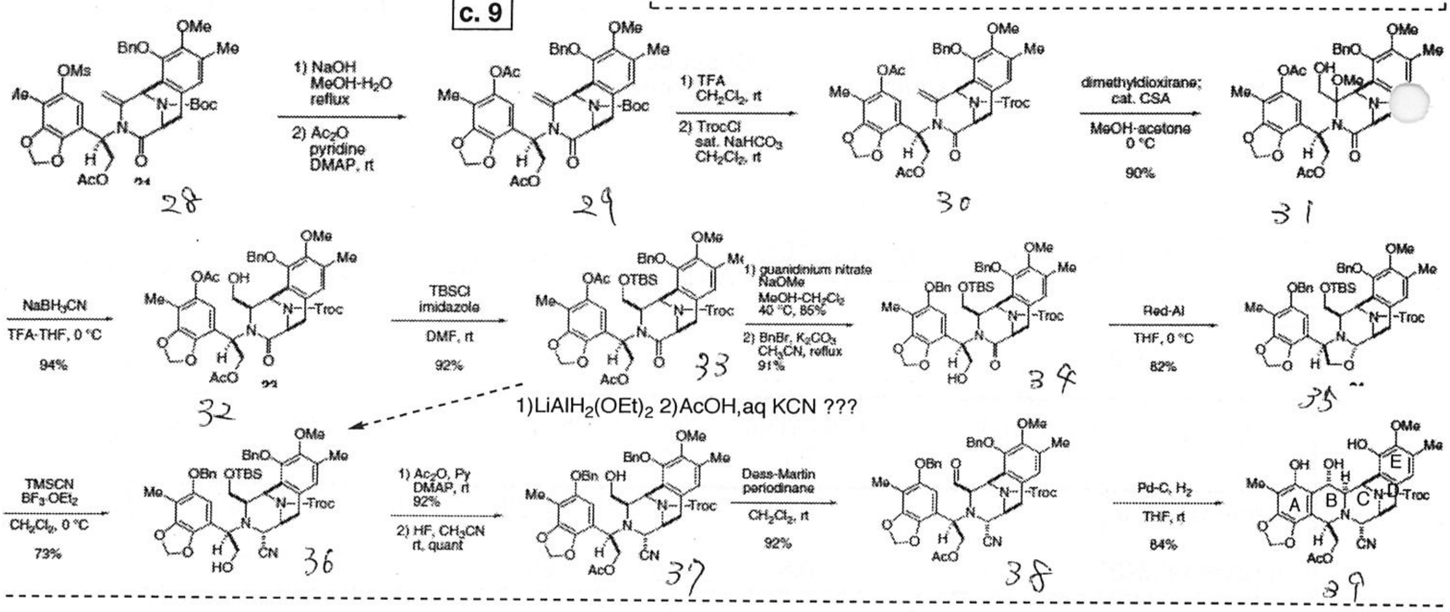



<Construction of D ring> y. 65%




<Construction of B ring> y. **18%**

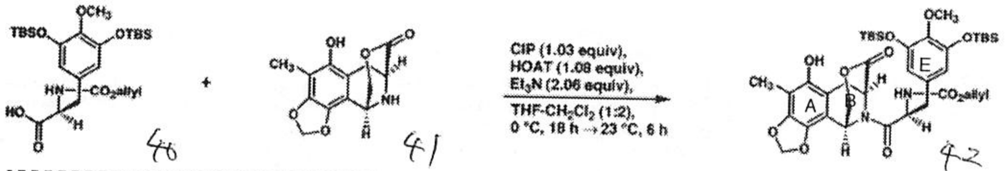
a. 2
b. 4
**c. 9**



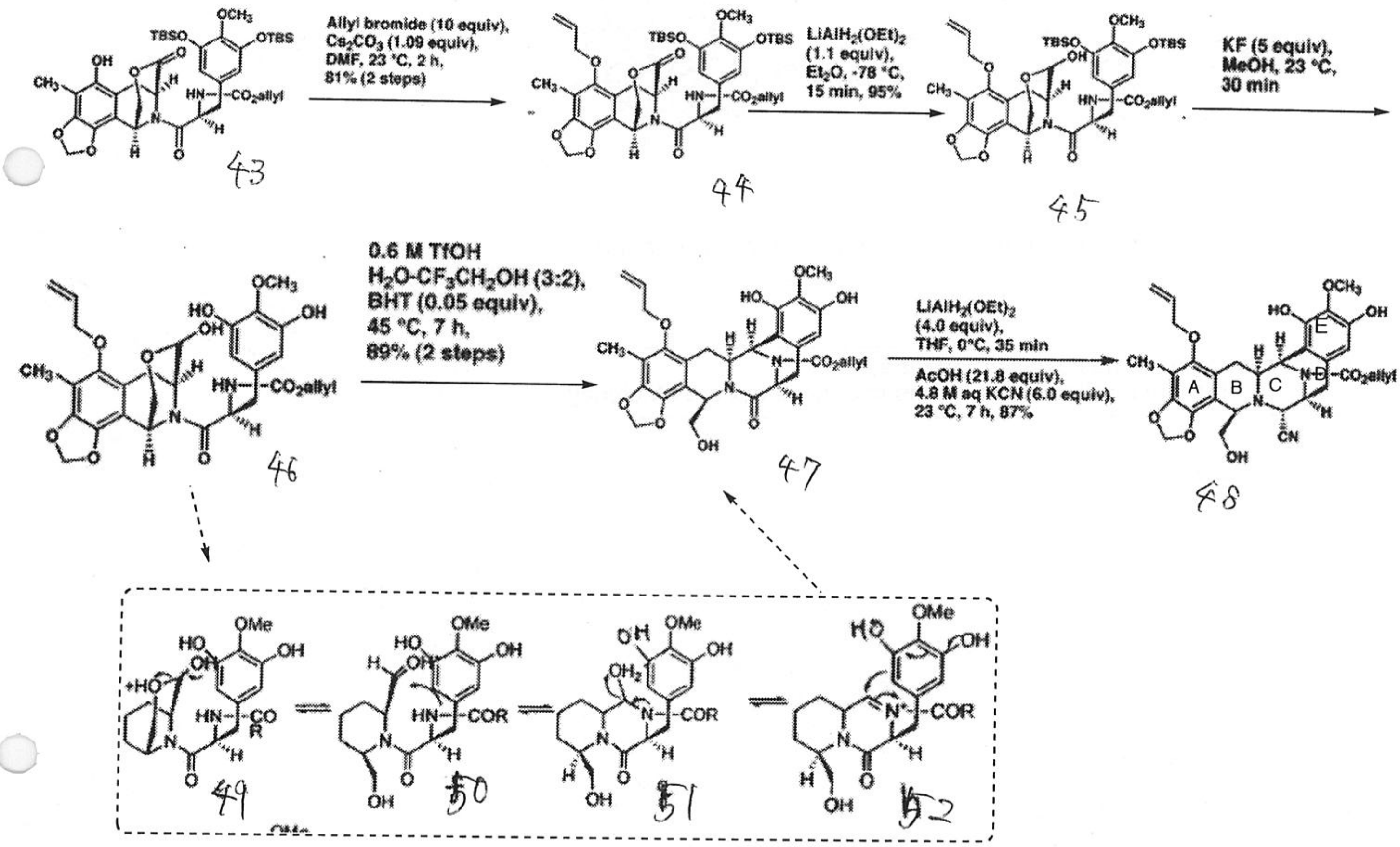

**This B ring construction results in low yield(18%), and this seems to cancell out MCR's "economy"**
**(alternative --► reaction can shorten the synthetic scheme ??? )**

## Corey's route

<Construction of A, B, E ring> y.81%




<Construction of C,D ring> y.74%



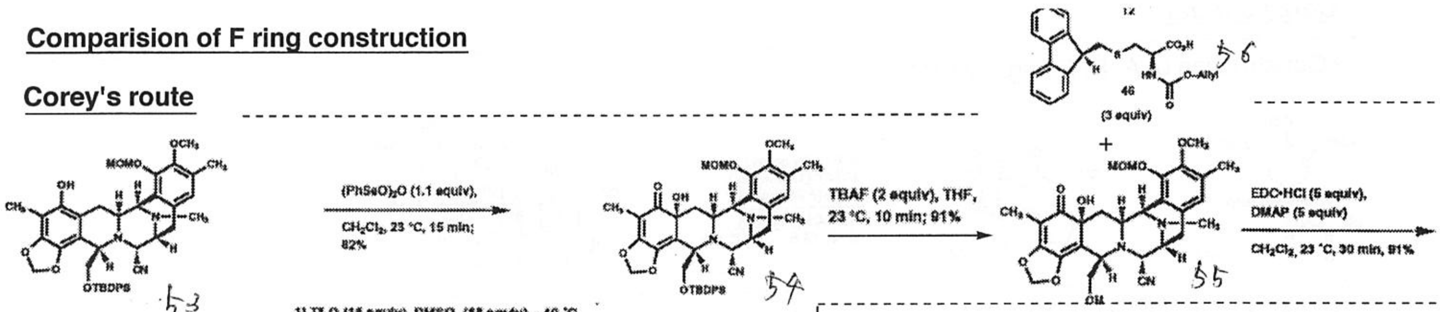

**Corey exceeds Fukuyama in "economical" Mannich-type Cascade Reaction in terms of yield.**

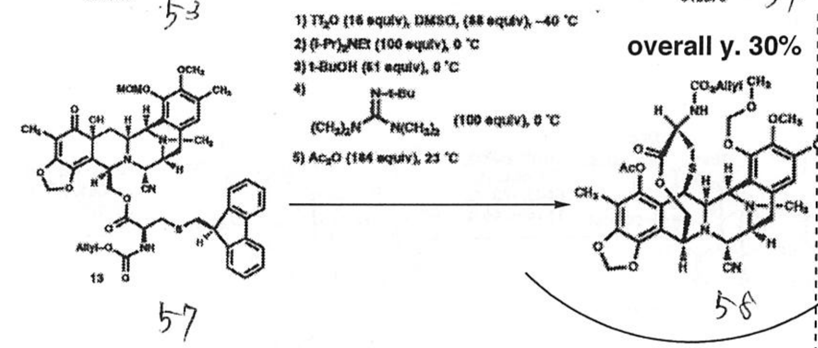
**Although Corey's route does not have the freshness such as "Fukuyama's MCR",**

**Corey's route realizes the "justice=economic" required for MCR and Cascades.**

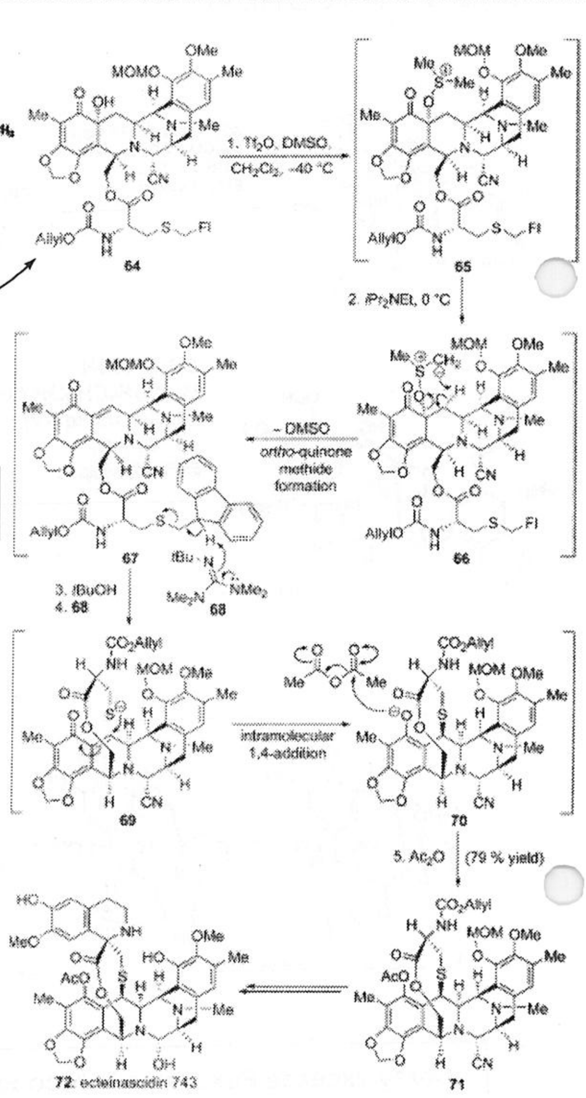
## Comparision of F ring construction

### Corey's route



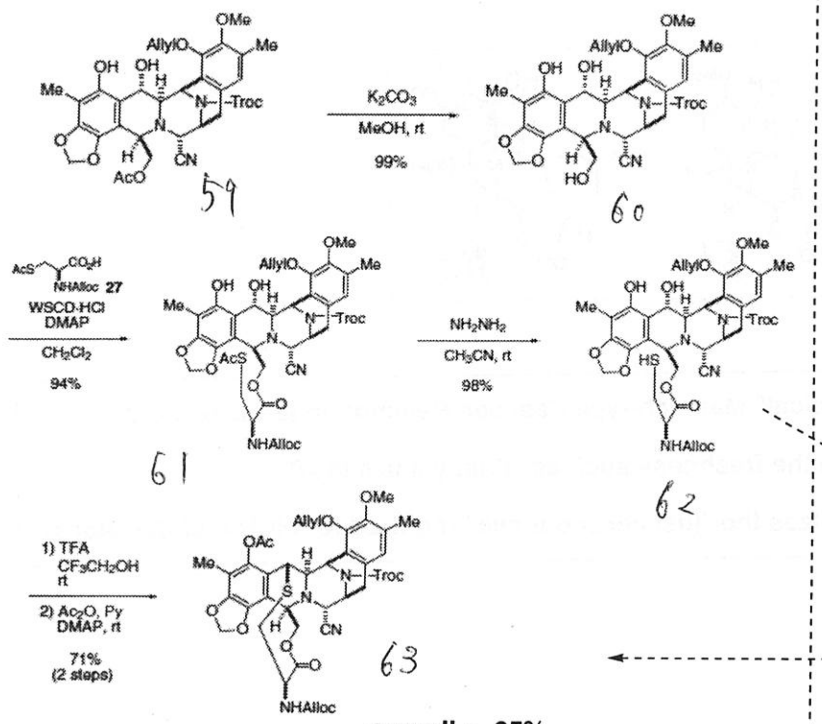

overall y. 30%



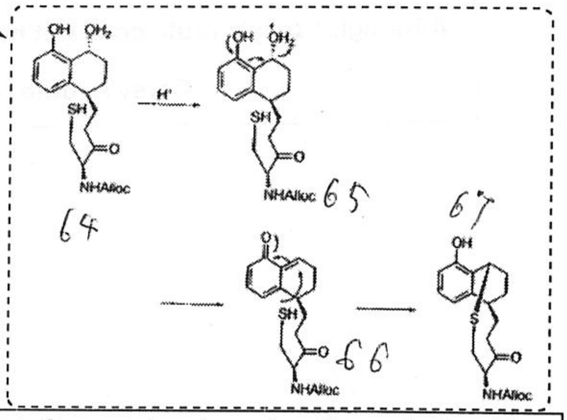

**Key Reaction = Michael type Cascade reaction**

> This reaction itself has excellent feature,
> but preparation steps seems to cancell out the efficiency.

### Fukuyama's route




**overall y. 65%**




> **Fukuyama exceeds Corey in F ring construction although his step also can be viewed as Cascade Reaction.**

## Conclusion

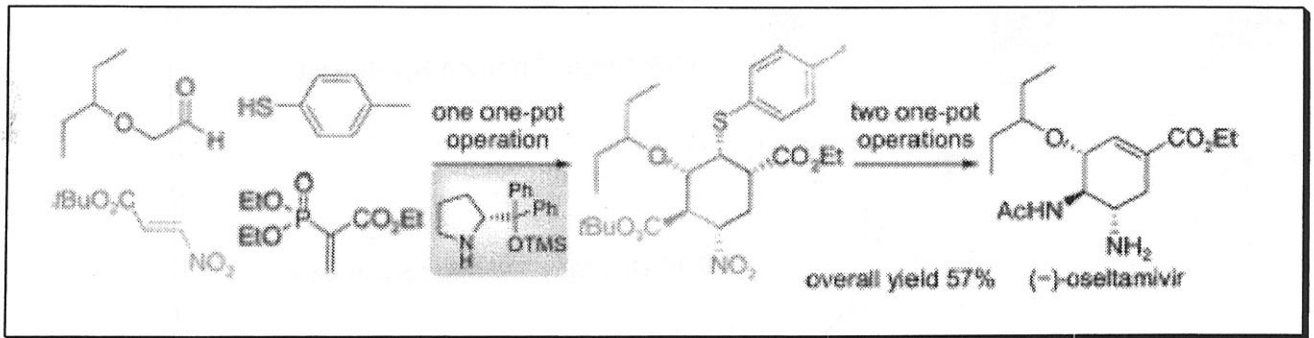
**Comparison&evaluation between 2 routes suggest that**

- **Corey's route turned to be the most efficient in terms of "economy"**
  **(that includes total steps, yields, C-X forming steps).**
- **Fukuyama's fascinating MCR seems to be eliminated by other ineffectual steps.**
  **(including preparating steps for MCR)**
- **Fukuyama and Corey's routes are actually never impressive from the "economical" point of view,**
  **but intensive in these point "applications for total synthesis ", "intellectual reaction itself ",I think.**

| Routes | Total Steps | Total Yields (%) | A~E (%) | Key (%) | C-X (%) | Protect/Deprotect (%) |
|---|---|---|---|---|---|---|
| **Corey(cascade)** | **34** | **1.7** | **16** | **74, 30** | **38** | **44** |
| **Fukuyama(MCR)** | **50** | **0.8** | **2.7** | **90** | **26** | **56** |
| **Zhu (convergent)** | **23** | **3.0** | | | | |

## 2. (-)- Oseltamivir ~Efficient application of MCR ~

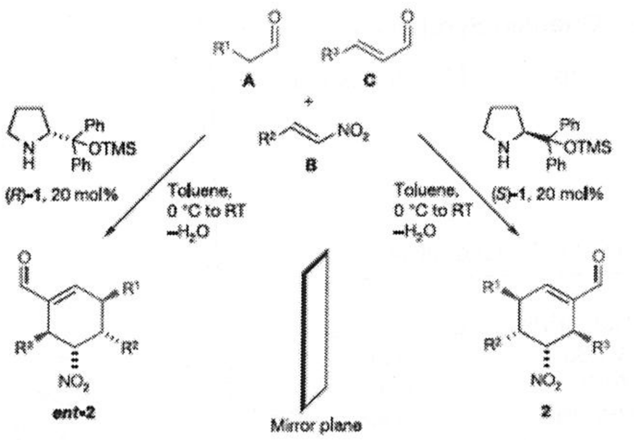
Hayashi.Y et al. *ACIE*.**2008**, early view

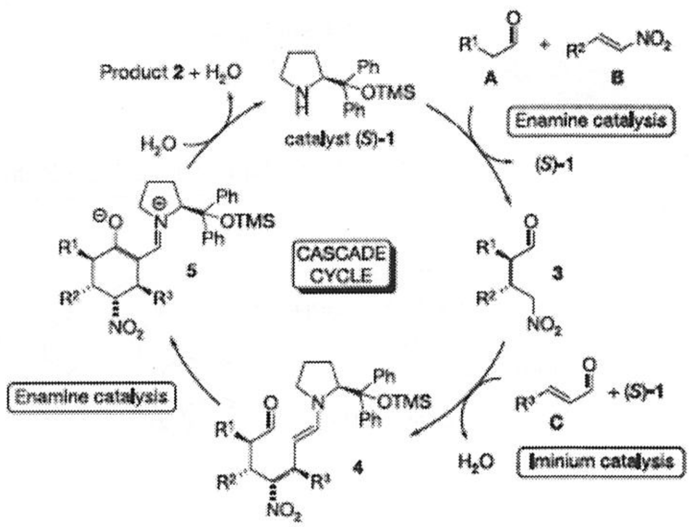



This synthesis can be the most suitable model
to show the powerfullness of MCRs !!!

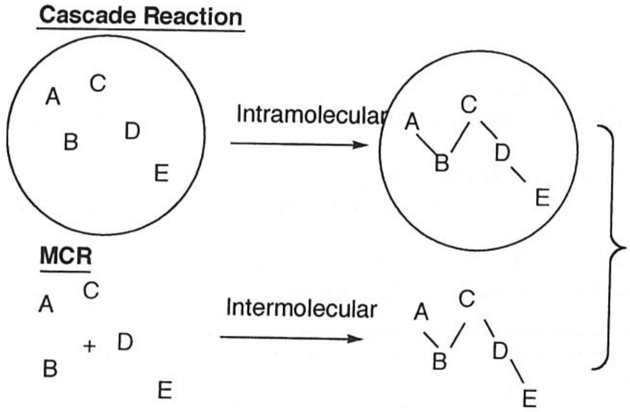
(although I think such a case is very rare and lucky.)

Enders et al. *Nature*. **2006**, 441, 861



# 4. My feelings through the study




Both are actually powerful reactions
to achieve atom, step, all efficiencies.

but...(for total synthesis)

Both requires appropriate target molecules
preparation operations to set appropriate positions
distortions of other steps

⇩

**This would cancel out the efficiency of the reaction.**

**5 "stop and go" synthesis can exceed 1 MCR in terms of "economical justice")**

Both have no generalities to apply all compounds, reactions.

⇩

Each specific application to complex molecules should be the seeds of new chemistry.

Generallity
↓
Accumulation of each reaction

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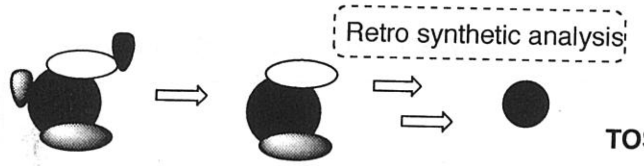


**TOS(Target-Oriented Synthesis)**

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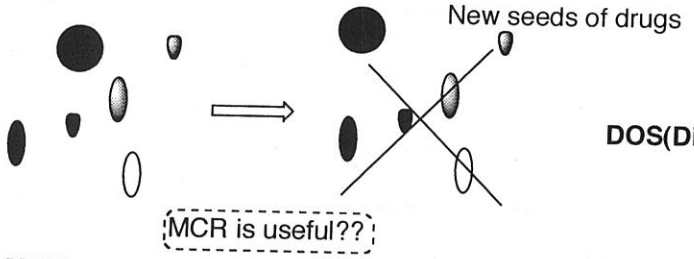


**DOS(Diversity-Oriented Synthesis)**

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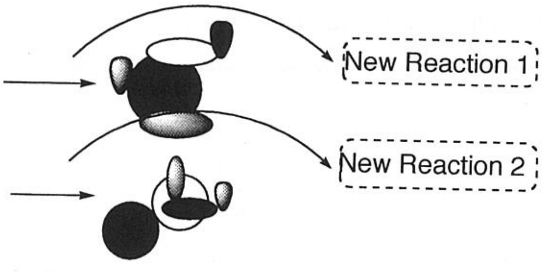
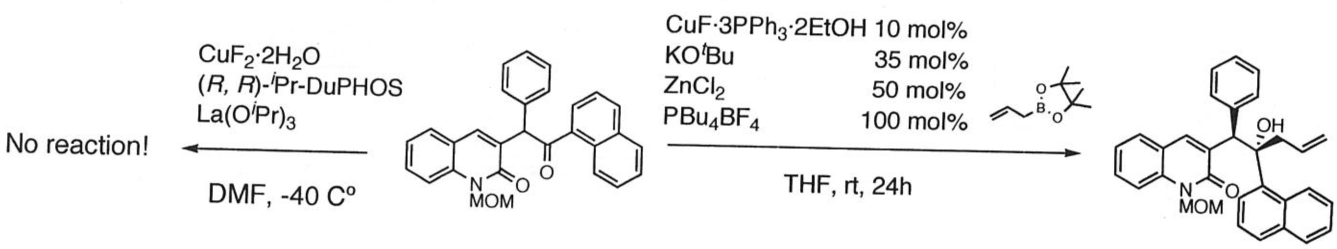



**ROS(Reaction-Oriented Synthesis)**

(discussion with Mr.Yamatsugu)

ex) My reserch topic Diastereoselective Cu-catalyzed allylation




**quant dr = up to 5/1**

**Especially MCRs are never revolutionally fresh concept,**
**but do have possibility to synthesize complex molecules in one pot.**

MacMillan *synlett*, **2007,** 10, 1477