Journal Club Dec. 1st, 2011

Motoharu Oiki

Collective synthesis of natural products by means of organocascade catalysis

Spencer B. Jones, Bryon Simmons, Anthony Mastracchio and David W. C. MacMillan

Nature, **2011**, *475*, 183-188

1. Introduction

1.1 Two significant remaining challenges in the field of total synthesis

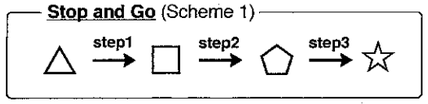
- Large-scale production of biologically important molecules
- Synthesis of large collections of natural product families or their analogues

1.2 Synthesis of natural products; artificial vs. biological

- Artificial synthetic methods (conventionally employed methods)

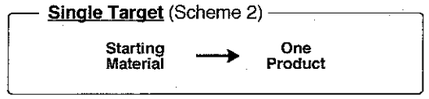
(1) 'Stop-and-go' process

- Individual transformations are conducted as stepwise (**Scheme 1**).



(2) 'Single-target' approach

- One target product through one synthetic approach (**Scheme 2**)



- Biosynthesis in nature

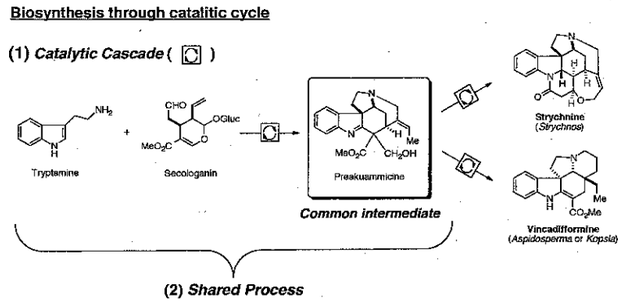


Figure 1. Prekuammicine serves as a biosynthetic precursor to a range of structurally diverse member of the *Strychnos*, *Aspidosperma* and *Kopsia* alkaloid families. Gluc, glucose.

(1) Enzymatic cascade reactions involving coupling and skeletal rearrangement
=> Afford short access to target products

(2) Differently-structured molecules are produced from a common intermediate.
=> Because the intermediate is synthesized from the same starting materials and through the same catalysis, resources are used efficiently.

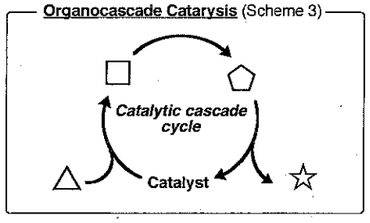
1.3 This Work

- Two concepts inspired by biosynthesis

(1) Organocascade Catalysis

- Catalytic cycle involving several structural transformations (**Scheme 3**)

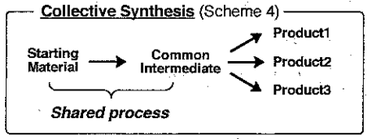
=> Short-step and enantioselective synthesis



(2) Collective Synthesis

- The preparation of structurally diverse natural products from common intermediate (**Scheme 4**)

=> Economical production of natural products



- To demonstrate this approach, they conducted total synthesis of six well-known alkaloids using organocascade catalytic reaction (**Figure 2**).

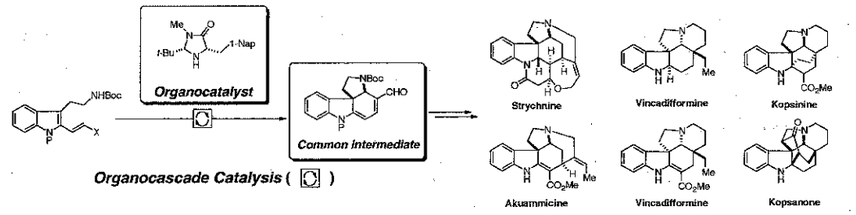


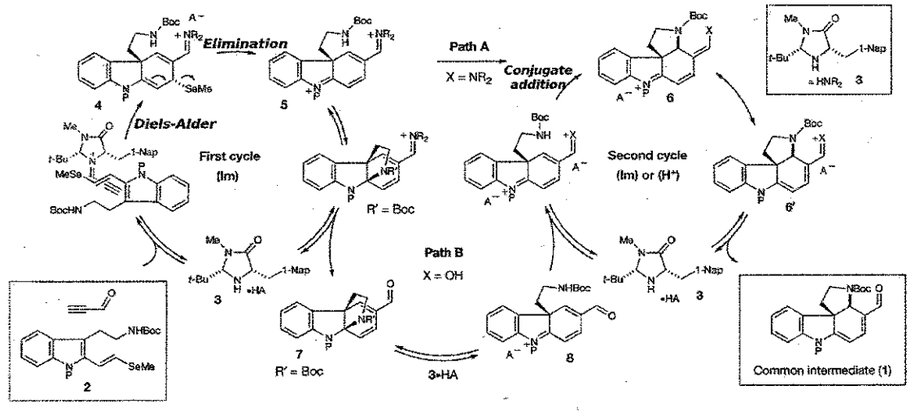
Figure 2. Collective synthesis with organocascade catalysis.

2. Results and Discussion

2.1 Organocascade catalytic reaction

- A one-flask, asymmetric organocascade catalytic reaction
- Diels-Alder reaction; Elimination reaction; Conjugate addition reaction

- Authors proposed two paths of mechanism (**Figure 3**).



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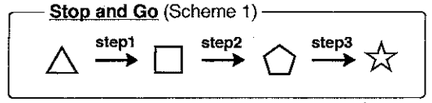

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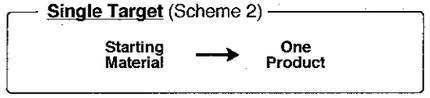

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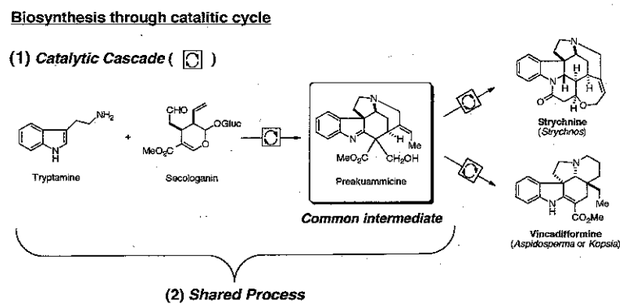

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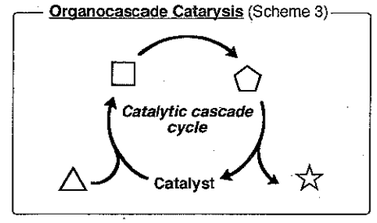

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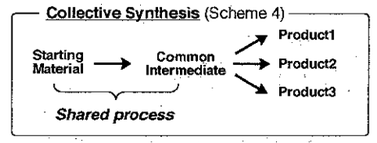

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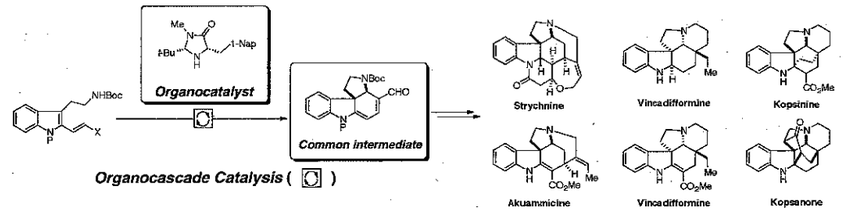

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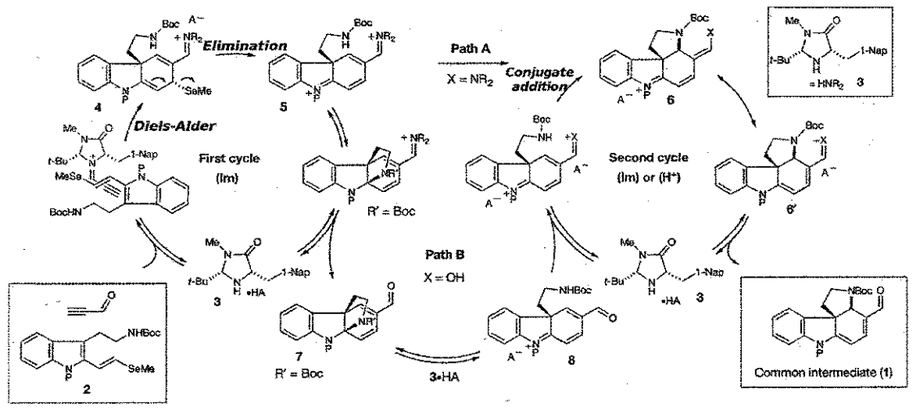

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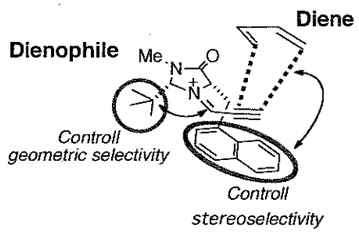


Diels-Alder reaction (2+3 -> 4)

• Bulky tert-butyl (*t*-Bu) group pushes away the acetylenic moiety.
=> Geometric selectivity of the dienophile

• Naphthyl group shields the bottom face of the reacting alkyne
=> Stereoselectivity of the Diels-Alder reaction

Figure 4. Selectivity of Diels-Alder reaction.

Elimination (4 -> 5)

• The cycloadduct **4** would undergo β-elimination of methyl selenide..

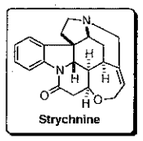
Conjugate addition (5 -> 1; Path A, X=NR_2)

• Iminium-catalized 5-*exo*-heterocylization would be expected to occur at the δ-position to the indolinium ion to deliver the spiroindoline core (**1**).

Conjugate addition (5 -> 1; Path B, X=OH)

• Iminium **5** might undergo facile cyclization at the indoline carbon to generate pyrroloindoline **7** transiently, and then 5-*exo*-heterocylization would also give **6**.

2.2 Total synthesis of strychnine



• Synthesis of strychnine has been the focus for over 50 years.
• This target is considered as a key metric for the success of their strategy.

9 -> 11

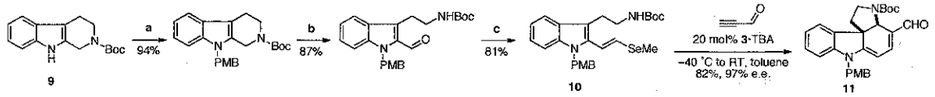


Figure 5. **a,** NaH, PMBCl, dimethylformamide (DMF), 0 °C. PMB, *para*-methoxybenzyl. **b**, SeO_2, dioxane, H_2O, 100 °C. **c**, $(EtO)_2P(O)CH_2SeMe$, 18-crown-6, potassium bis(trimethylsilyl)amide (KHMDS), tetrahydrofuran (THF), –78 °C to room temperature (RT, 23 °C). e.e., enantiomeric excess.

• 2-Vinyl indole **10** was prepared in three steps from commercially available **9**.
• Organocascade addition-cyclization was accomplished with imidazolidinone catalyst in the presence of tribromoacetic acid (TBA) co-catalyst (97% e.e.).

11 -> 14

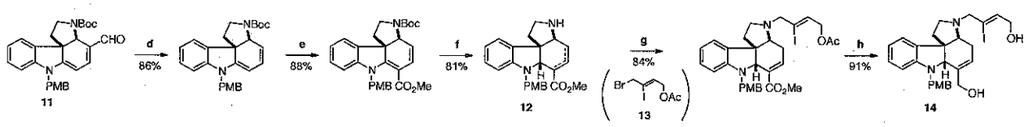


Figure 6. **d**, $(Ph_3P)_3RhCl$, toluene, PhCN, 120 °C. **e**, $COCl_2$, Et_3N, toluene, –45 °C to RT, then MeOH, – 30 °C to RT. **f**, DIBAL-H, CH_2Cl_2, –78 °C to RT, then trifluoroacetic acid (TFA), –78 °C to RT. **g**, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), K_2CO_3, DMF, (*Z*)-4-bromo-3-iodobut-2-enyl acetate (**13**), RT. **h**, DIBAL-H, CH_2Cl_2, –78 °C. Ac, acetyl.

• Step **d** to **f**: decarbonylation with Wilkinson's catalyst, induction of a carbomethoxy group, reduction of enamine unsaturation through the use of DIBAL-H.
• The following two-step protocol involves allylation with the substituted allyl bromide **13** and DIBAL-H-mediated reduction of both ester groups.

14 -> Strychnine

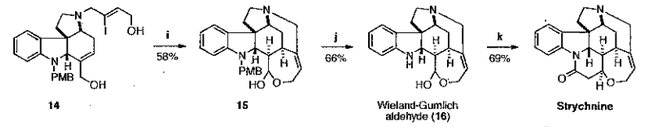
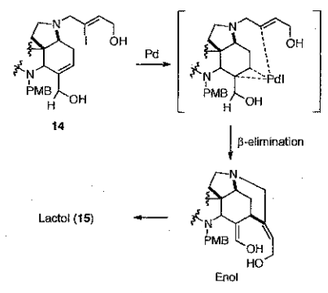


Figure 7. **i**, 25 mol% Pd $(OAc)_2$, Bu_4NCl, $NaHCO_3$, EtOAc, RT. **j**, PhSH, TFA, 45 °C. **k**, NaOAc, Ac_2O, AcOH, malonic acid, 120 °C.



• As a second key step, vinyl iodide **14** was converted to the protected Wieland-Gumlich aldehyde **15** through a cascade Jeffery-Heck cyclization/lactol formation sequence. PMB protecting group is critical in facilitating regioselective β-hydride elimination away from the indoline ring methine.
• The synthetic sequence was completed by TFA-mediated removal of the PMB group, to furnish **16**, which delivered enantioenriched (–)-strychnine in 12 steps and 6.4% overall yield.

2.3 Demonstration of collective synthesis

• Authors achieved in total synthesis of six well-known compounds of the *Strychnos*, *Aspidosperma* and *Kopsia* families of alkaloids (**Figure 8**).
• Total synthesis exhibited unprecedented levels of efficiency.

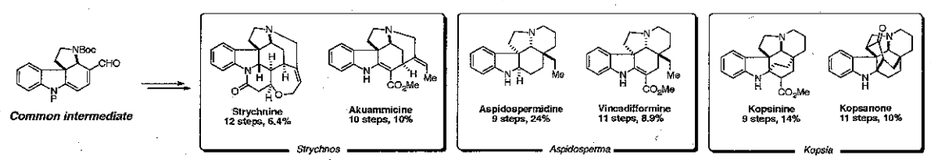


Figure 8. The chemical structure of alkaloids synthesized in this report, and the number of steps and yield. Each percentage denotes overall yield. Alkaloids in three different families were synthesized from a common intermediate tetracycle.

3. Conclusion

• Authors demonstrated the capabilities of collective total synthesis in combination with oraganocascade catalysis.
• This synthetic strategy would provide researchers with the tools to gain ready access to large collection of complex molecular architectures.