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Total Synthesis of Solanoeclepin A

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1. Introduction

1.1 Potato cyst nematode (PCN)

•Causes severe crop losses in potato production.

•Cyst (left of ***Figure 1***)→ Strong barrier of PCN eggs against external environment.

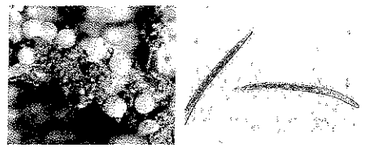


Figure 1. Potato cyst nematode

➔Make it difficult to exterminate PCN by agricultural chemicals.

•Juvenile PCN (right of ***Figure 1***) – Very short life in the absent of host plant.

➔Extermination by hatching stimulus is promising.

1.2 Solanoeclepin A

•Solanoeclepin A, which is excreted by the potato roots, shows significant hatching-stimulating activity toward PCN.

•Synthetic challenges of Solanoeclepin A

(1)ABC ring system: stereochemistry of oxacycloheptanone (AB ring) and highly functionalized seven-membered ring (C ring).

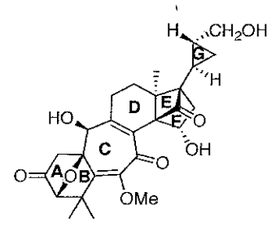


Figure 2. The structure of Solanoeclepin A

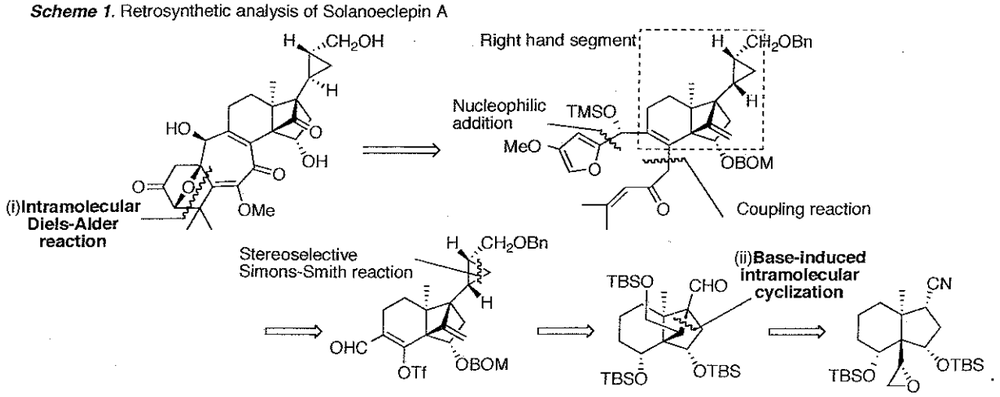
(2)DEF ring system: highly strained and stereochemically dense tricyclodecane skeleton.

1.3 This article

•First total synthesis of Solanoeclepin A

•Key reactions are (i)stereoselective construction of E ring by base-induced intramolecular cyclization[1] (ii) one-step synthesis of ABC framework by intramolecular Diels-Alder reaction.

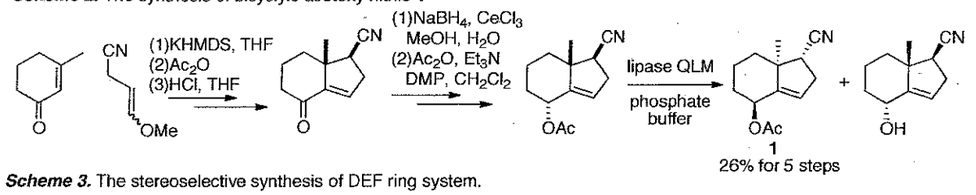
Scheme 1. Retrosynthetic analysis of Solanoeclepin A



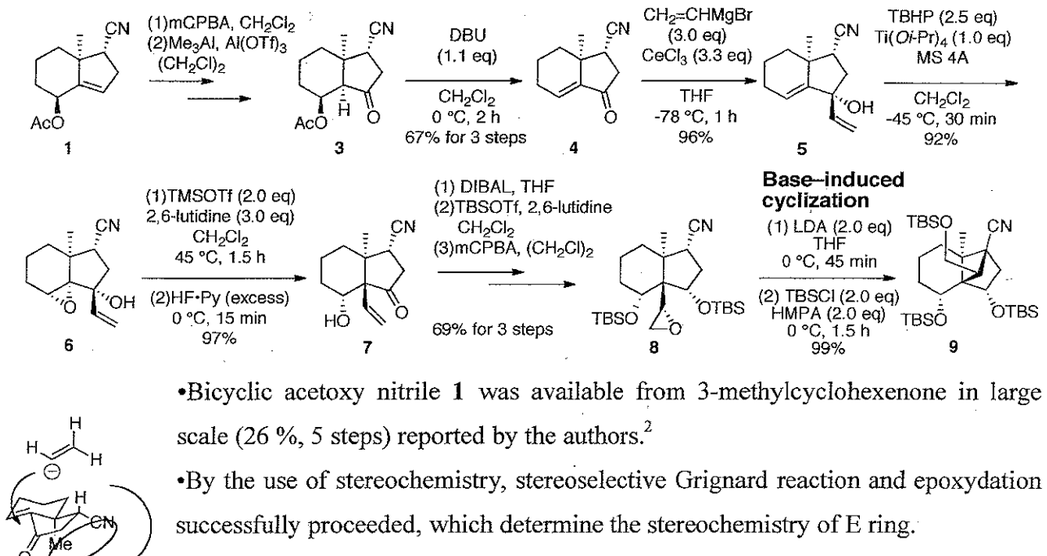
2. Results and discussion

2.1 Stereoselective synthesis of DEF ring system (*Scheme 2* and *3*).

Scheme 2. The synthesis of bicyclyic acetoxy nitrile **1**



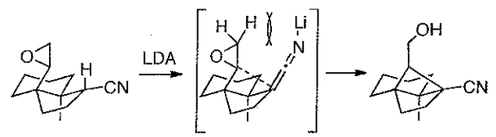
Scheme 3. The stereoselective synthesis of DEF ring system.



•Bicyclic acetoxy nitrile **1** was available from 3-methylcyclohexenone in large scale (26 %, 5 steps) reported by the authors.[2]

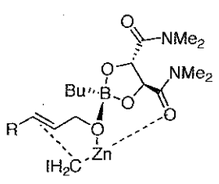
•By the use of stereochemistry, stereoselective Grignard reaction and epoxydation successfully proceeded, which determine the stereochemistry of E ring.

•The key base–induced cyclization reaction formed desired DEF ring system in excellent yield.



•The steric hindrance of allenic structure allowed epoxy nitrile **8** to form E ring system.

2.2 Synthesis of right-hand segment **17** (***Scheme 4***).

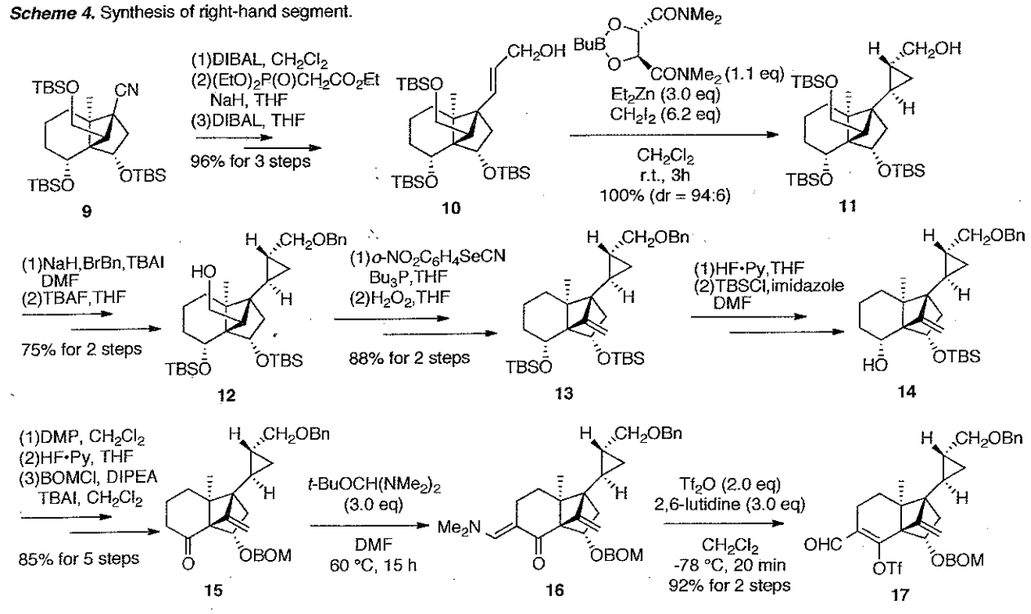


•By the use of chiral dioxaborolate ligand, stereoselective Simons-Smith reaction successfully proceeded.[3]

•Hydroxy groups were selectively protected or functionalized for the next ABC ring formation steps.

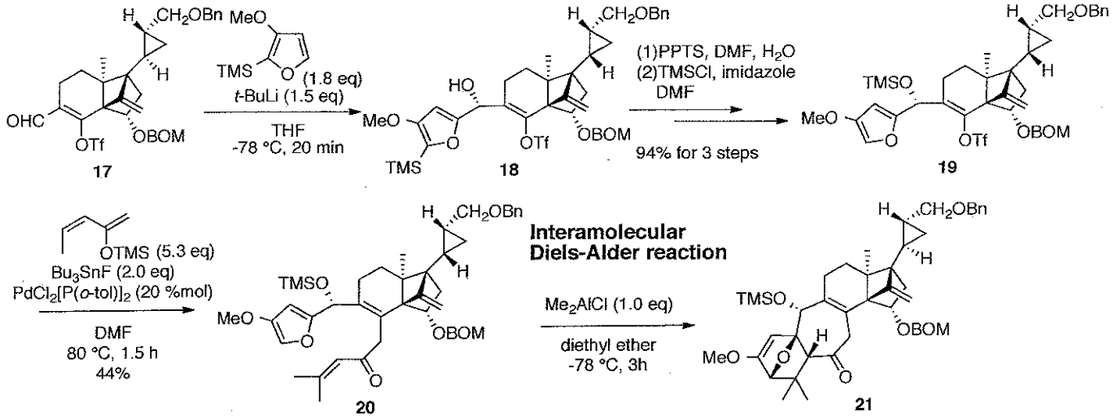
•The right-hand segment **17** was synthesized in 47% from compound **9**.

Scheme 4. Synthesis of right-hand segment.

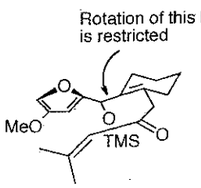


2.3 Synthesis of ABC ring system (*Scheme 5*).

Scheme 5. Intramolecular Diels-Alder reaction for the synthesis of ABC ring system



•The precursor **20** for intramolecular Diels-Alder reaction was synthesized by the use of two functionalized positions on six-membered ring of compound **17**.[4]

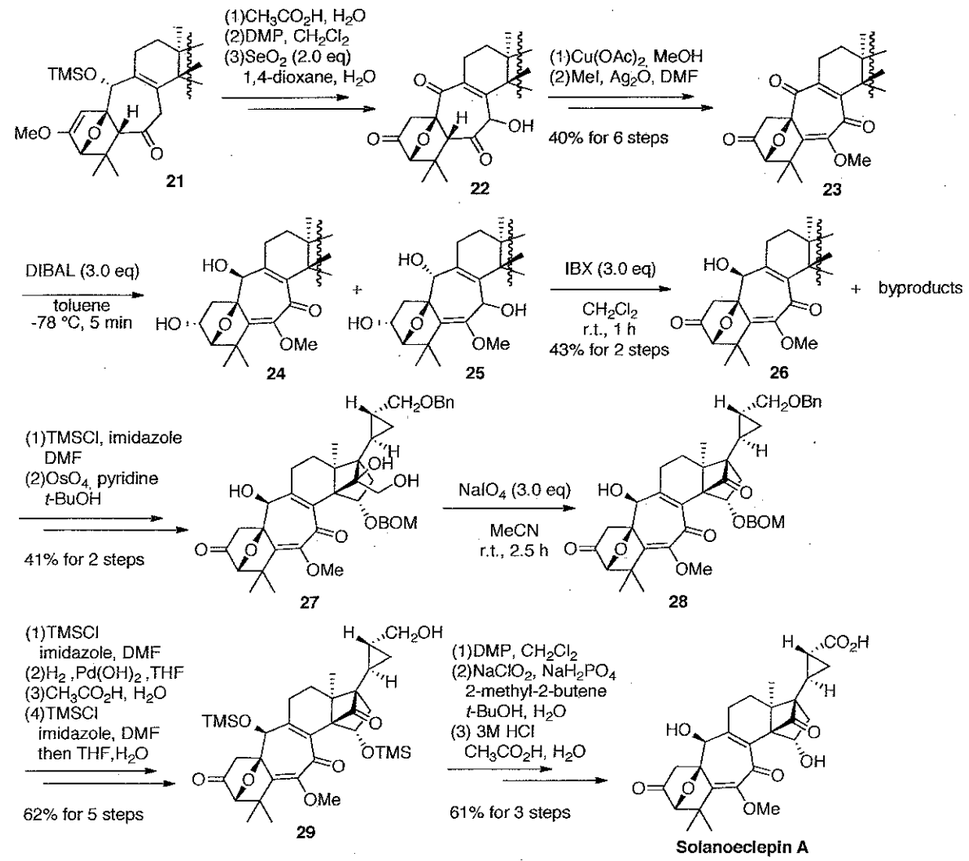


•The key reaction for the synthesis of ABC ring system is intramolecular Diels-Alder reaction, which can construct ABC ring system in one step.

•Steric hindrance between the TMS group and the cyclohexene ring restricts rotation, which successfully led to desired stereostructure of AB ring.

2.4 Synthesys of Solanoeclepin A (*Scheme 6*)

Scheme 6. Synthesis of solanoeclepin A



•The yield of desired stereostructure compound **26** was low because of .low stereoselectivity of reduction of ketone **23**.

•After the terminal alkene moiety was converted into ketone **28**, selective protection and oxidation afforded Solanoeclepin A successfully.

3.Conclusion

Solanoeclepin A was synthesized in 0.18% yield in 52 steps, starting from 3-methylcyclohexenone. The total synthesis of solanoeclepin A was achieved for the first time by the two key intramolecular cyclization reactions.

4.Reference

1. Stork, G.; Cama, D, L.; Coulson, D, R. *J. Am. Chem. Soc.* **1974**, *96,* 5270-5272.
2. Tanino, K.; Tomata, Y.; Shiina, Y.; Miyashita, M. *Eur. J. Org. Chem.* **2006**, 328-334.
3. Charette, A,B.; Juteau, H.; Lebel, H.; Molinaro, C. *J. Am. Chem. Soc.* **1998**, *120,* 11943-11952.
4. Kuwajima, I.; Urabe, H. *J. Am. Chem. Soc.* **1982**, *104,* 6831-6933.