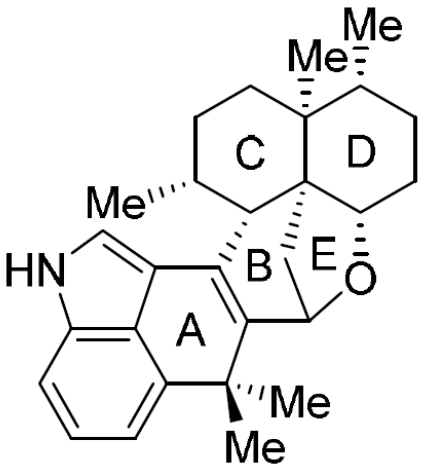
Total Synthesis of Epoxyeujindole A

Zhaohong Lu, Hailong Li, Ming Bian, and Ang Li

J. Am. Chem. Soc., DOI: 10.1021/jacs.5b09198



epoxyeujindole A

Highy substituted A B rings:
sequential cationic cyclizations

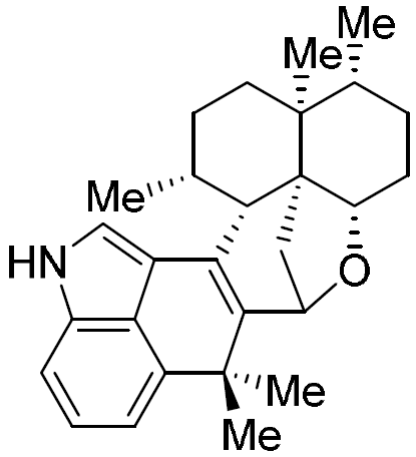
Liming Cao

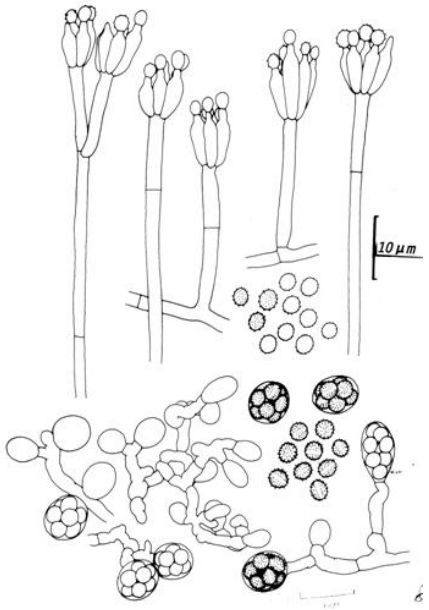
Wipf Group Current Literature

10/24/2015

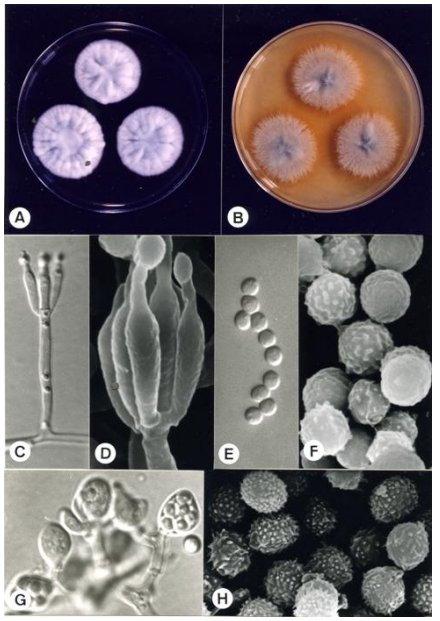
Indole Terpenoids from *Eupenicilium Javanicum*

- Indole terpenoids comprise a large number of biologically and biosynthetically interesting natural products.
- Nakadate et al. in 2011 reported the isolation of Epoxyeujindole A from *Eupenicilium Javanicum.*
- Its absolute configuration was not determined.





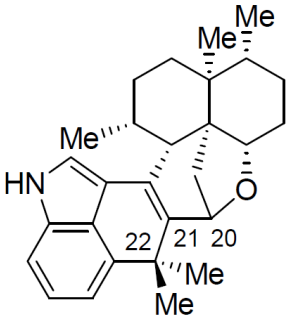
penicilli, conidia, asci, and ascospores



A, B. colonies on CYA And MEA at 25 °C, 7 d; C, D. penicillus; E, F. conidia; G. asci; H. ascispores

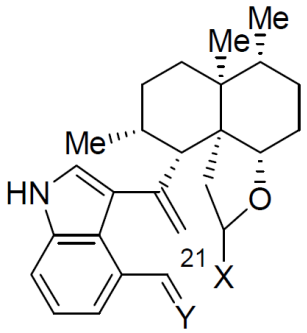
In *Recent Advances in Phytochemistry*, Vol. 40, Romeo, J.T., Ed.; Elsevier, 2006; pp 1–22
Heterocycles **2011**, *83*, 351. *Heterocycles* **2011**, *83*, 1867
http://www.bcrc.firdi.org.tw/fungi/fungal_detail.jsp?id=FU200802030002

Retrosynthetic Analysis of Epoxyeujindole A



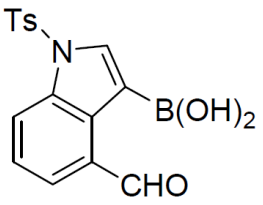
4: epoxyeujindole A

key disconnections:
C20-C21; C21-C22;
electron rich exocyclic
olefin: sequential Prins
cyclizations



5

Suzuki–Miyaura
coupling



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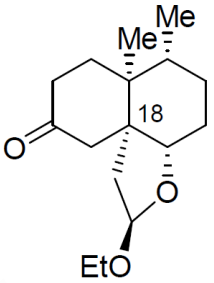
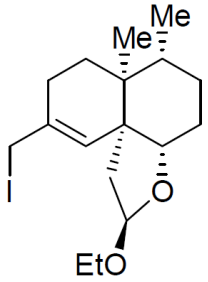


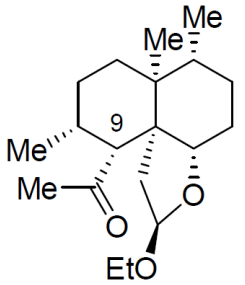
9

Stille-Migita
coupling



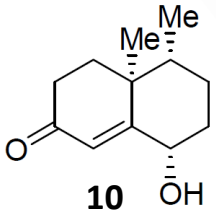
8

Nozaki–Hiyama
–Kishi coupling
with acetaldehyde



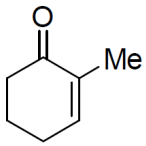
6

Tetrahydrofuran motif
bearing C18:
Luche cyclization



10

assymetric conjugation
and alkylation



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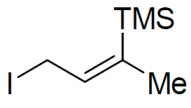

12

$AlMe_3$

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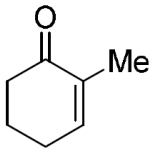
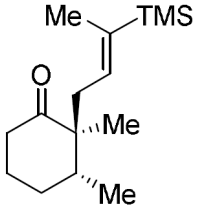


11

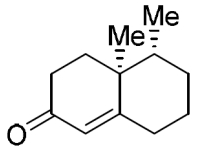
a) Me_3Al (1.2 eq), CuTC (2 mol%), **14** (4 mol%), Et_2O, −30 °C, 2.5 h;
-
MeLi (1.0 eq), HMPA (2.5 eq), −30 °C, 20 min; **12** (1.3 eq), THF, −30 °C, 24 h, −10 °C, 24 h, 0 °C, 48 h, 65%



15
3.8:1 dr

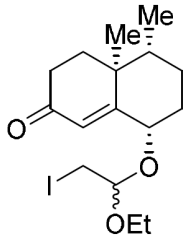
(Trapping the enolate with methyl vinyl ketone was inefficient(<20%) due to polymerization.)

b) K_2CO_3 (2.0 eq), *m*-CPBA (1.2 eq), CH_2Cl_2, 0 °C, 1.5 h;
c) TFA/CH_2Cl_2, 0 °C, 15 min;
-
d) MeONa (3.0 eq), MeOH, 22 °C, 2.5 h, 53% (3 steps);



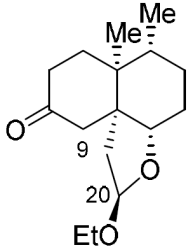
16 (95% ee)

e) $HC(OMe)_3$ (18 eq), TsOH (15 mol%), DMF, 10 °C, 2 h;
f) Oxone (1.0 eq), −5 °C, THF, 1.5 h, 51% (2 steps);
-
g) NIS (6.0 eq), ethyl vinyl ether (8.0 eq), CH_2Cl_2, 0 °C,1.5 h, 94%;



17

h) Zn (9.0 eq), CuI (2.7 eq), pyridine/water (1:4), 22 °C, 2 h, 68%;
-
i) MsOH (20 mol%), EtOH, 22 °C, 1 h, 89%;



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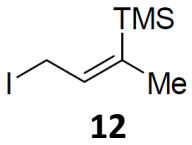

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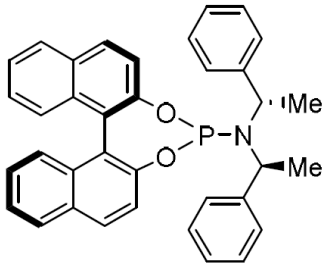
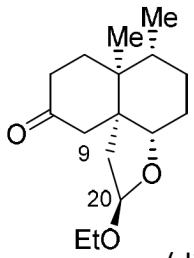


(*R*, *S*, *S*)**-14**

J. Am. Chem. Soc., DOI: 10.1021/jacs.5b09198

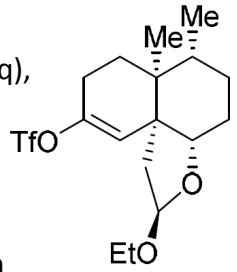
Total Synthesis of epoxyeujindole A



9

j) LiHMDS (2.3 eq),$PhNTf_2$(1.9 eq),
THF, −78 °C, 10 min, 87%;

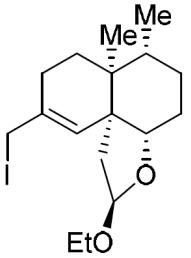
(directing effect: the ethyloxy oxygen through chelation with Li/base aggregates)



18

k) $Pd(PPh_3)_4$ (10 mol%), Bu_3SnCH_2OH (2.0 eq),
LiCl (2.0 eq), THF, 65 °C, 2 h;

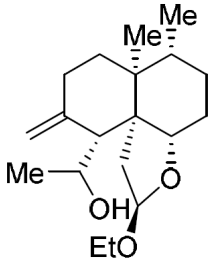
l) PPh_3 (1.2 eq), I_2 (1.2 eq), imidazole (3.0 eq),
CH_2Cl_2, 0 °C, 30 min, 81% (2 steps);



8

m) $CrCl_2$ (5.0 eq), LiI (1.2 eq),
2,6-lutidine (10 eq), MeCHO (21 equiv),
22 °C, 5 h, 67%;

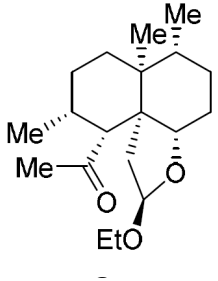
(2,6-lutidine: buffer)



19

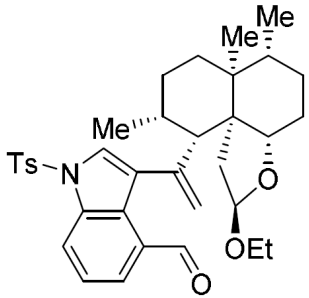
n) Raney Ni, H_2 (60 bar),
EtOH, 22 °C, 1 h;

o) TPAP (10 mol%), NMO(3.0 eq),
CH_2Cl_2, 22 °C, 30 min, 91% (2 steps);



p) KHMDS (1.1 eq), $PhNTf_2$ (1.8 eq),
THF, −30 °C, 10 min;

q) $Pd(PPh_3)_4$ (10 mol%), $NaHCO_3$ (1.6 eq),
7 (1.5 eq), toluene/MeOH/water (4:1:1),
22 °C, 30 min, 51% (2 steps).



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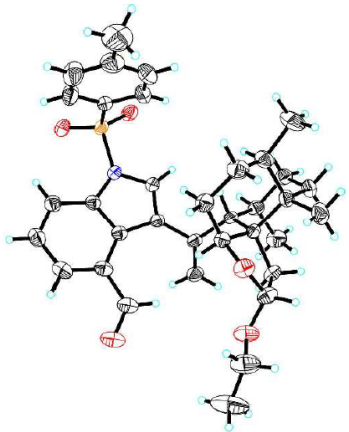

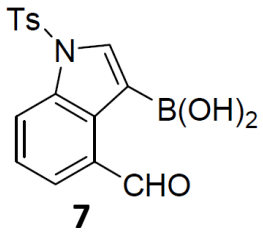

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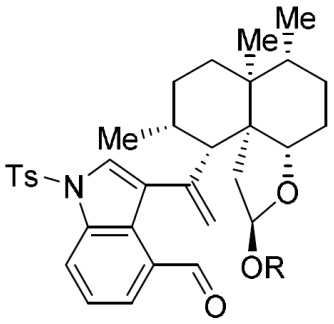
Total Synthesis of epoxyeujindole A

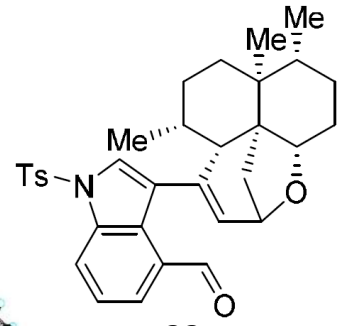
Double Prins strategy:



a) aq. HClO4 (0.50 M), THF, 22 °C, 8 h, 82%;

13: R = Et
21: R = H

b) TsOH (1.0 eq), CH_2Cl_2, 22 °C, 30 min, 76%;



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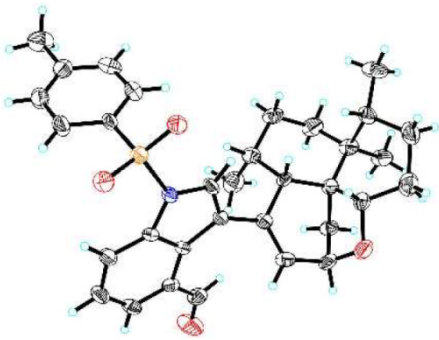
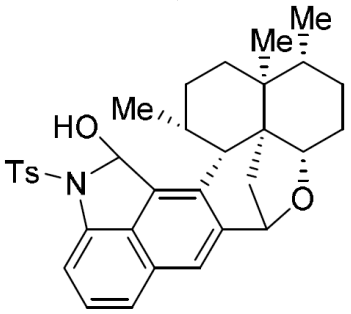
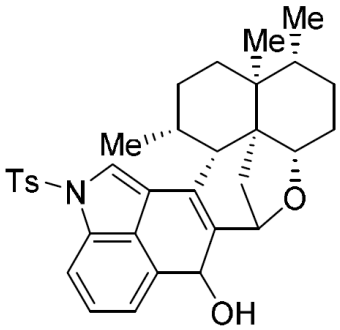


c) $BF_3 \bullet OEt_2$ (2.7 eq), CH_2Cl_2, 22 °C, 10 min, 72%.



23



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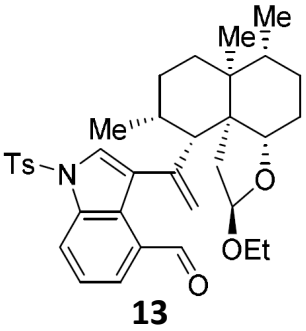
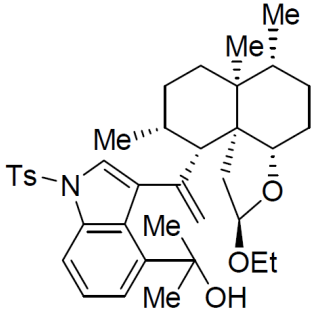


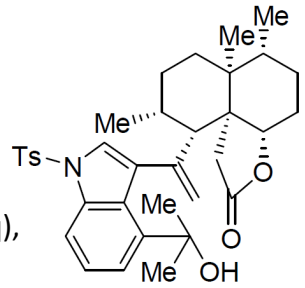
13

a) MeMgBr (2.3 eq), THF, −78 °C, 10 min;
b) TPAP (10 mol%), NMO (6.1 eq), CH_2Cl_2, 22 °C, 30 min;
c) MeMgBr (4.2 eq), $CeCl_3$ (5.0 eq), THF, 0 °C, 30 min, 85% (3 steps)



24

d) aq. $HClO_4$ (0.50 M), THF, 22 °C, 5 h;
e) TPAP (10 mol%), NMO (3.0 eq), CH_2Cl_2, 22 °C, 30 min, 95% (2 steps);



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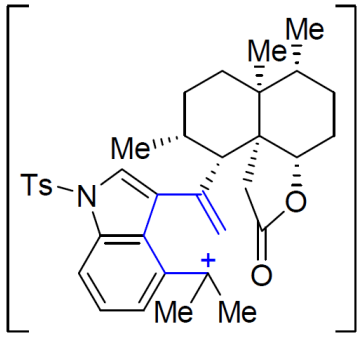
f) $BF_3 \bullet OEt_2$ (1.5 eq), $MeNO_2$, 75 °C, 5 min, 65%;



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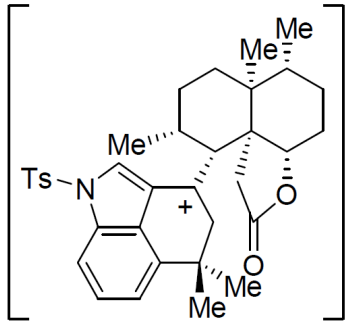

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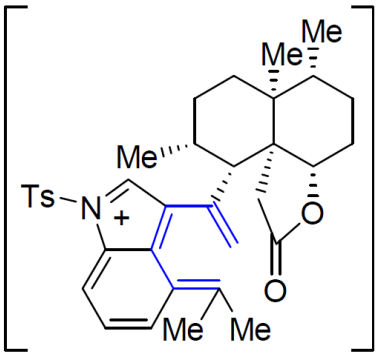

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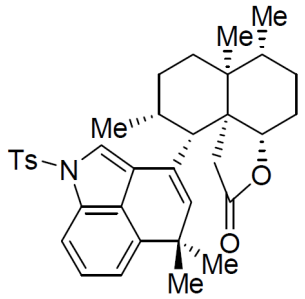

26

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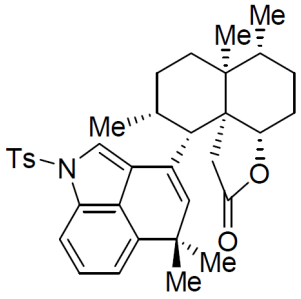
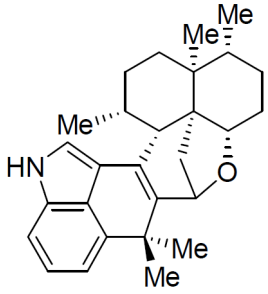
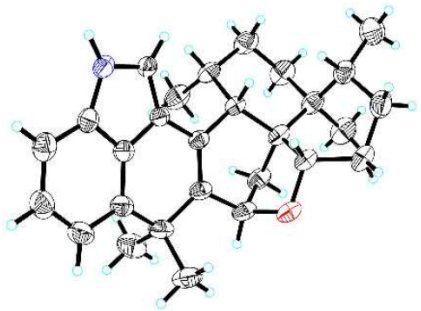


26

g) DIBAL-H (3.0 eq), CH_2Cl_2, −78 °C, 10 min;
h) TsOH (3.0 eq), CH_2Cl_2, 22 °C, 30 min;
-
i) Mg (19 eq), MeOH, 22 °C, 1 h, 84% (3 steps).



4: epoxyeujindole A



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Total Synthesis of epoxyeujindole A

- The first asymmetric synthesis of epoxyeujindole A was accomplished.
- The key C−C bond formations at an early stage include an enantioselective conjugate addition/alkylation, a Luche cyclization, a Nozaki−Hiyama−Kishi reaction, and a Suzuki−Miyaura coupling.
- The assembly of the highly substituted A and B rings relies on sequential cationic cyclizations.
- The synthesis provides an efficient access to epoxyeujindole A