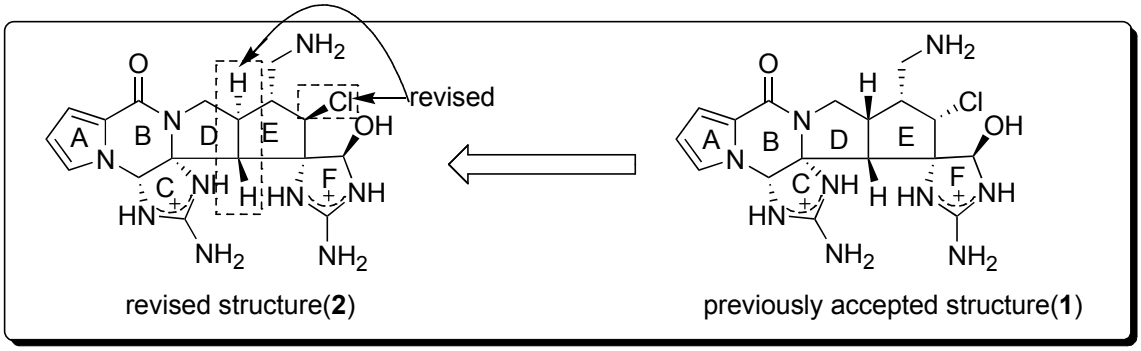
A. Nojiri (B4)
2. Feb. 2008. Sat

Palau'amine(Pyrrole-imidazole alkaloid family)



<Isolation>
From the sponge, *Stylotella aurantium* in the Western Caroline Islands.
(P. J. Scheuer et al. *J. Am. Chem. Soc.* **1993**, *115*, 3376)

<Structual determination>
Firstly, P.J. Scheuer determined structure as **1**. (P. J. Scheuer et al. *J. Am. Chem. Soc.* **1993**, *115*, 3376)
Revised structural determination(M. Kock et al. *Angew. Chem. Int. Ed.* **2007**, *46*, 2320
R. J. Quinn et al. *J. Org. Chem.* **2007**, *72*, 2309
S. Matsunaga et al. *Tetrahedron Lett.* **2007**, *48*, 2127)

<Bioactivity>
immunosupressive activity and low toxicity

<structual feature>
polycyclic framework containing
1) two spiroguanidine units
2) higly strained *trans*-azabicyclo[3,3,0]octane subunit.(D,E-ring)
3) All subsituted cyclopentane core containing spiro guanidine core(E-ring)

targeting palau'amine

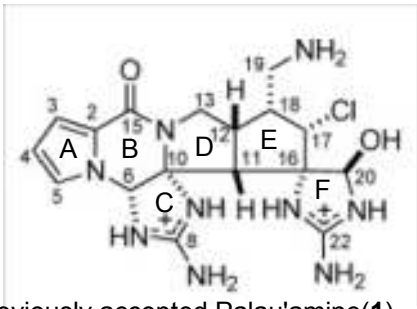
<Representative synthetic study>
M. Kock , P. S. Baran et al. *Angew. Chem. Int. Ed.* **2007**, *46*, 6586.
L. E. Overman et al. *J. Am. Chem. Soc.* **2007**, *129*, 12896.
and many others.(See reference above articles.)

< Total synthesis>
No report of successful total synthesis.

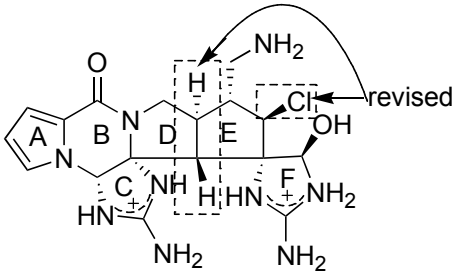
Overman,L.	Univ. of Cal, Irvine
Romo, D.	TAMU, TX
Austin, D. J.	Yale
Harran, P.	SWMED, Dallas, Tx
Chen, C.	SWMED, Dallas, Tx
Carreira, E.	ETH Switzerland
Baran, P. S	Scripps Institute
Gleason, J.	McGill, Canada
Horne, D	Oregon state uni.
Lindel, T	LMU, Germany
Shair, M	Harvard
Sorensen, E	Princeton
Williams , R	Colorado State
Ali, A	ICSN-France
Gin, D. Y	MSKCC
DuBois, J	Stanford University

contents

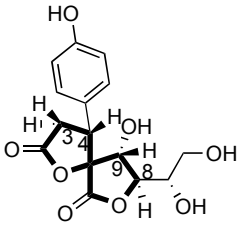
1. Why did relative configuration of the Palau'amine need revision?



previously accepted Palau'amine(**1**)



revised structure(**2**)



leucodrin(**3**)

1) The way of Scheuer's determination.

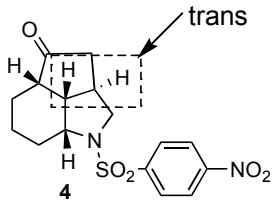
*Leucodrin(**3**)*
The coupling constants: 8.3 Hz (H8/H9) *trans*
7.8 Hz and 12.4Hz (H4/H3 + H3')

+

Palau's amine also has spiro ring.(ring E and F)
The coupling constant : 14.1 Hz (H11/H12).

⇩ ?

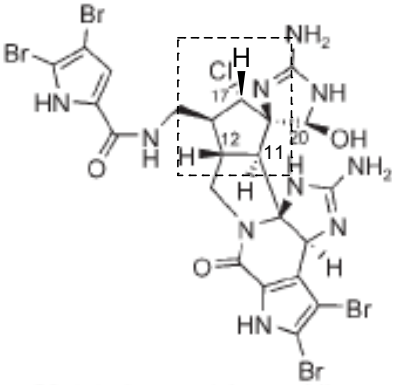
cis-fused structure



4

<The reason of misunderstanding the palau'amine structure>

1, Cis-fused 5,5-bicyclo ring is thermodynamically more stable.
2, Trans-fused annulated five-membered rings are quite rare.
Only 1 of 121 crystal structures is trans-fused.(compound **4**)
3. The coupling constant of Bicyclo[3,3,0]octanes were often not assigned, because the coupling constant couldn't be extracted from the multiplets.



22: tetrabromostyloguanidine

2) Kock's approach
22(similar spectra data to palau'amine and isolated from the same sponge)
ROESY spectra :weak signal(H11/H17)
strong signal(H12/H17)

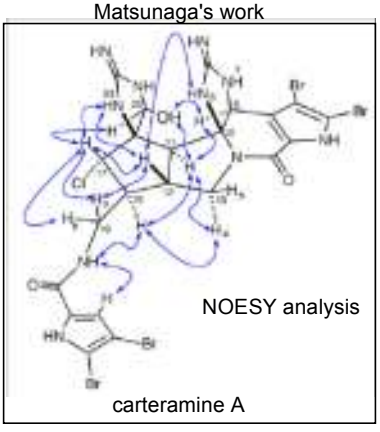
⇩ trans-fused ?

distance geometry(DG) and distance-bounds-driven dynamics(DDD) caluculations

⇩

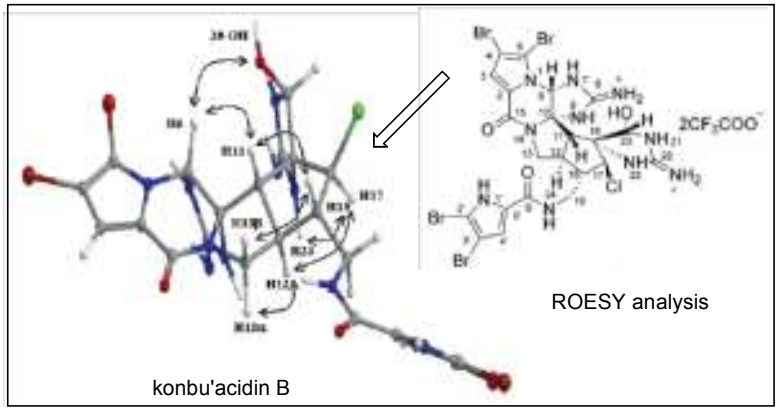
H11 and H12 must be trans-fused

Matsunaga's work



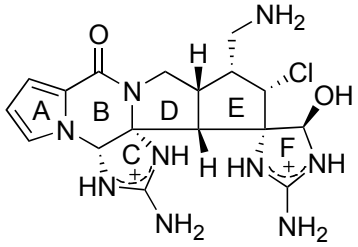
carteramine A

Quinn's work



konbu'acidin B

2. Synthetic study
i) Overman strategy



previous reported palau'amine(**1**)

J. Am. Chem. Soc. **2007**, *129*, 12896.

Overman's 4th report about palau'amine.

see also: *J. Am. Chem. Soc.* **1997**, *119*, 7159 (1st)

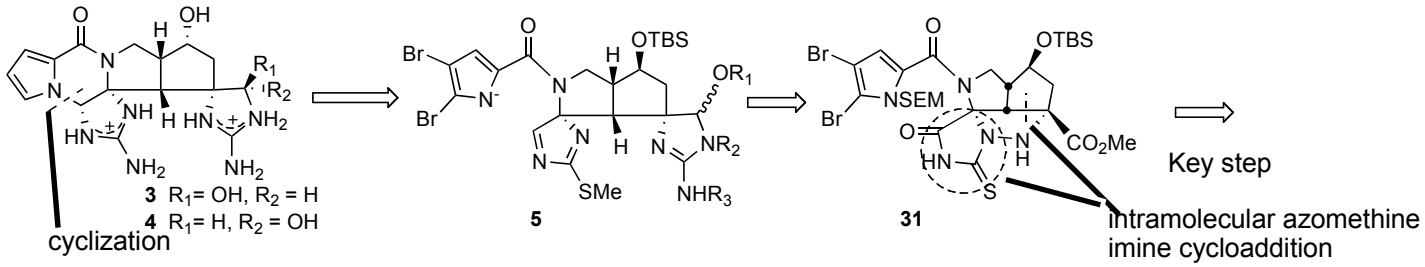
J. Org. Chem. **2002**, *67*, 7880 (2nd)

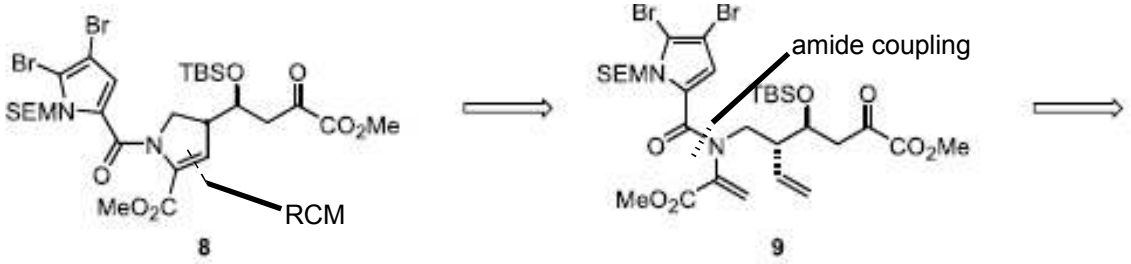
Tetrahedron **2004**, *60*, 9559 (3rd)

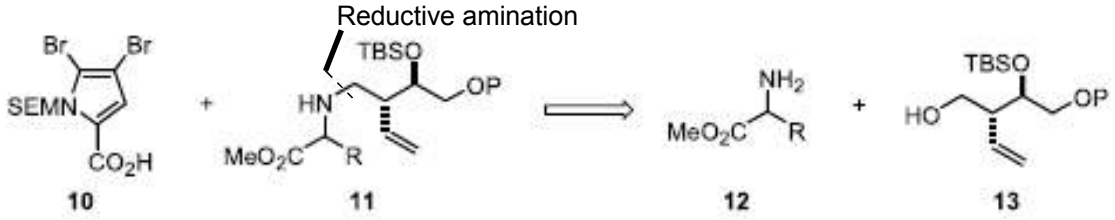
Before structure revised →
- abstract of each article
- 1st :First apply azomethine imine cyclization to Palau'amine core.
- 2nd:Tolerance of functional group.
- 3rd:Synthesis to intermedate 31.
- 4th:Synthesis to previous reported palau'amine core.

<Retrosynthesis analysis>

Overman tried to synthesize **3,4,** the analog of previous reported palau'amine(**1**)

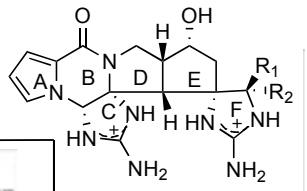




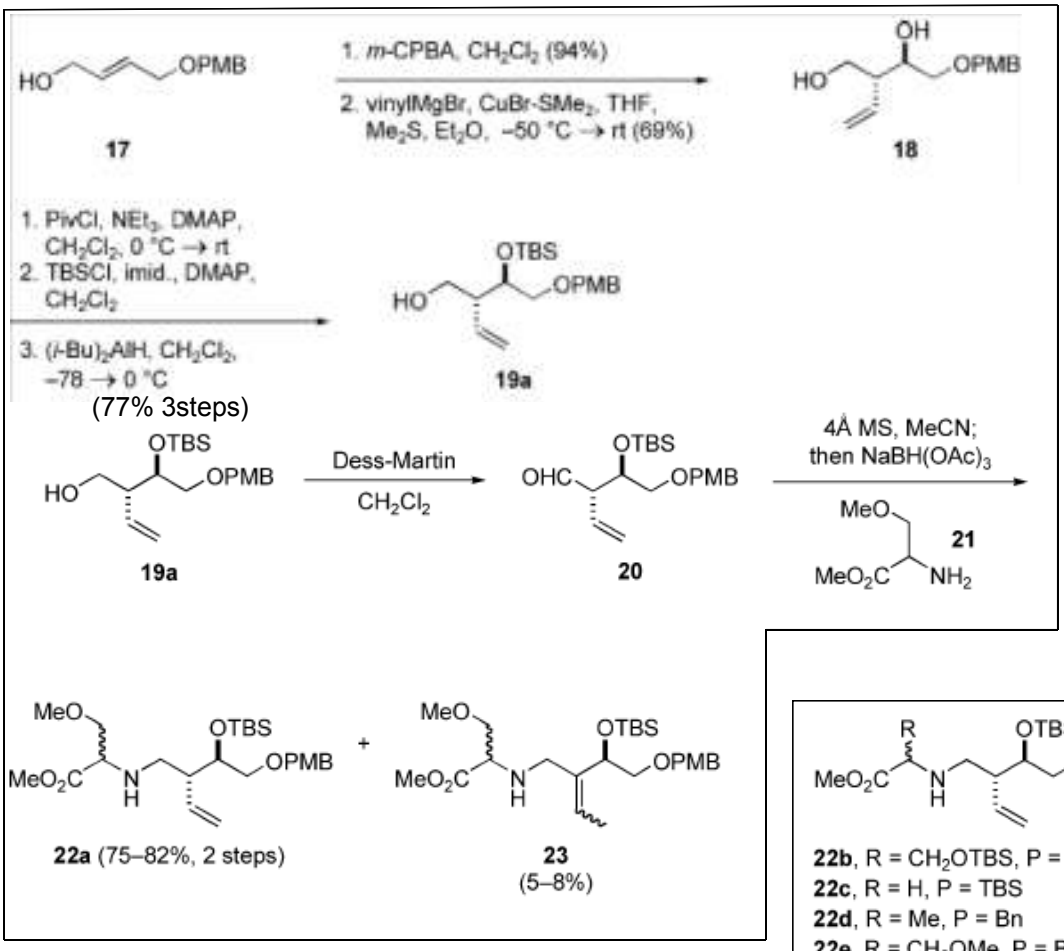


● Synthesis toward Palau's amine analog

1) preparation of substrate for RCM.

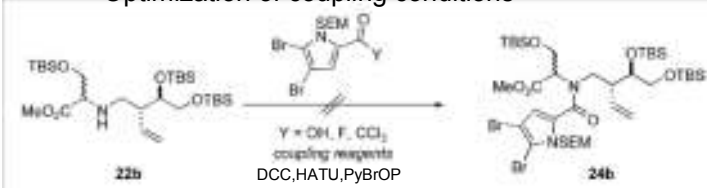


target compound



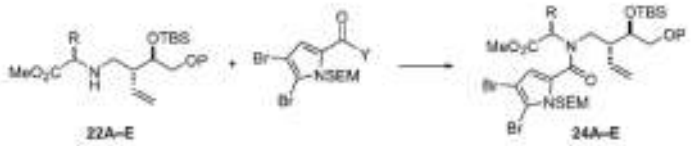
22b, R = CH_2OTBS, P = TBS
22c, R = H, P = TBS
22d, R = Me, P = Bn
22e, R = CH_2OMe, P = Bn

Optimization of coupling conditions



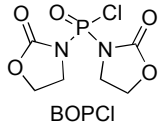
coupling reagents(DCC,HATU,PyBrOP)
>failed

Table 1.

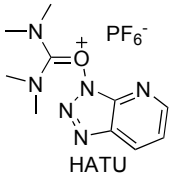


Amine	R	P	Y	Coupling agent	Amide	Yield (%)
22b	CH_2OTBS	TBS	OH	PyBrOP[a]	24b	0
22c	H	TBS	OH	PyBrOP[a]	24c	95
22d	Me	Bn	OH	PyBrOP[a]	24d	78
22e	CH_2OMe	Bn	OH	PyBrOP[a,b]	24e	0
22e	CH_2OMe	Bn	OH	HATU[c]	24e	0
22e	CH_2OMe	Bn	OC_6F_5	NA[d]	24e	0
22e	CH_2OMe	Bn	OH	BOPCl[e]	24e	87
22a	CH_2OMe	PMB	OH	BOPCl[e]	24a	>95

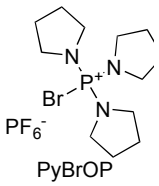
[a] PyBrOP, *i*-Pr_2NEt, DMAP, CH_2Cl_2, rt.
[b] PyBrOP, *i*-Pr_2NEt, DMAP, DMF, rt.
[c] HATU, HOAt, *i*-Pr_2NEt, DMF, rt.
[d] *i*-Pr_2NEt, DMAP, CH_2Cl_2 or NaH, THF, rt.
[e] BOPCl, *i*-Pr_2NEt, MeCN, 0 °C to rt.



BOPCl

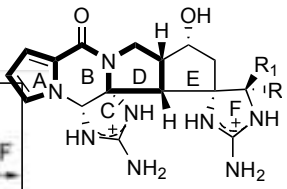


HATU

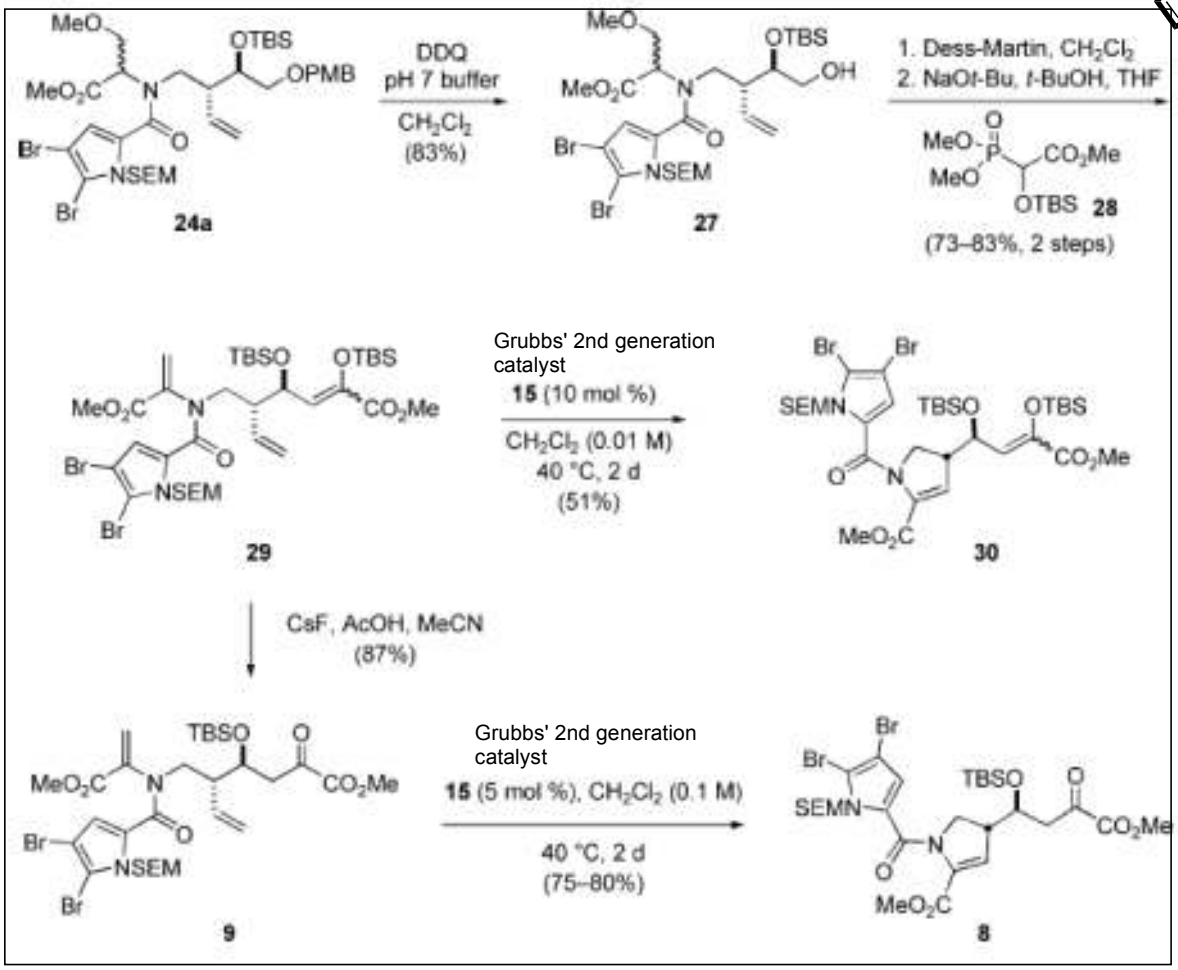


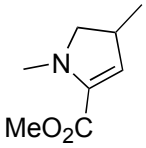
PyBrOP

2) synthesis of **8 (**D ring)



target compound



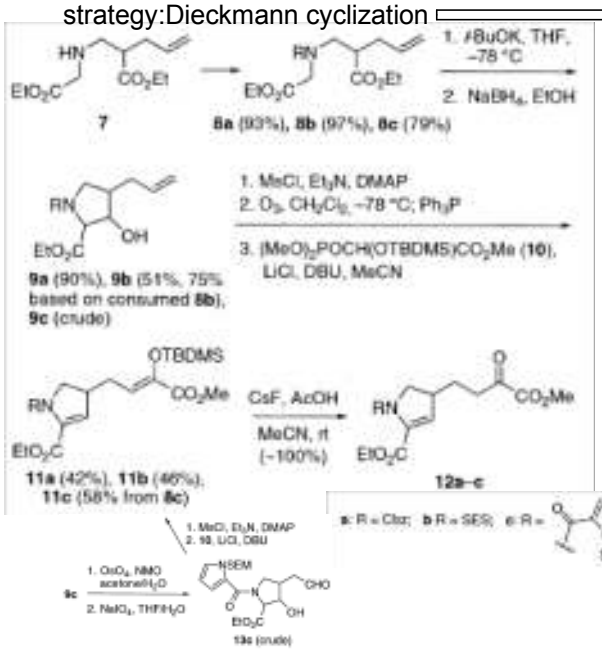


4,5-dihydropyrrole-2carboxylate moiety.

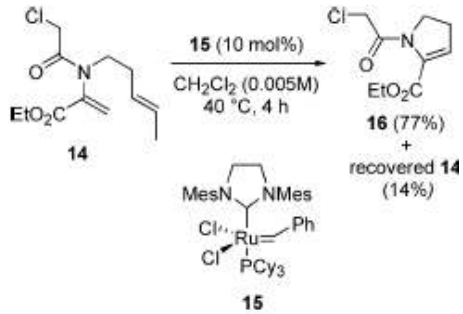
Previously reported strategy:Dieckmann cyclization

failed

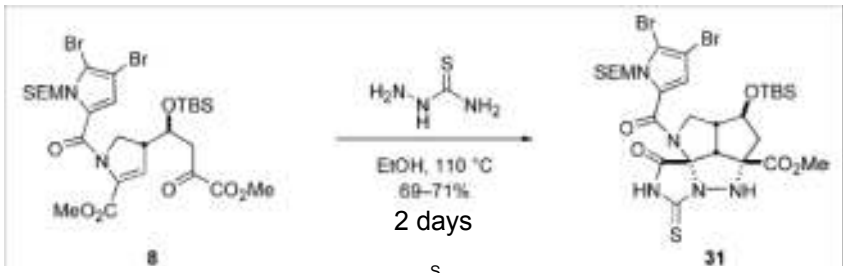
This time strategy: RCM

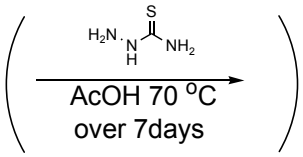


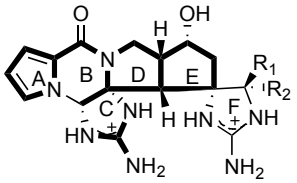
model substrates for RCM



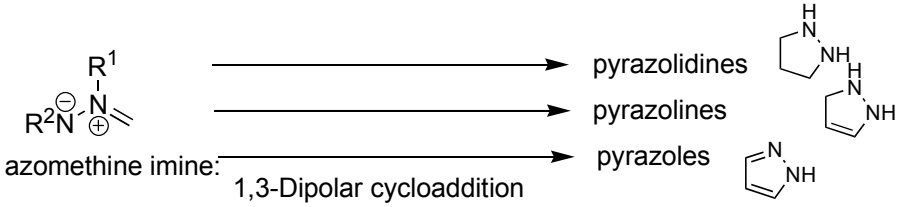
3) Key step Azomethine imine cyclization

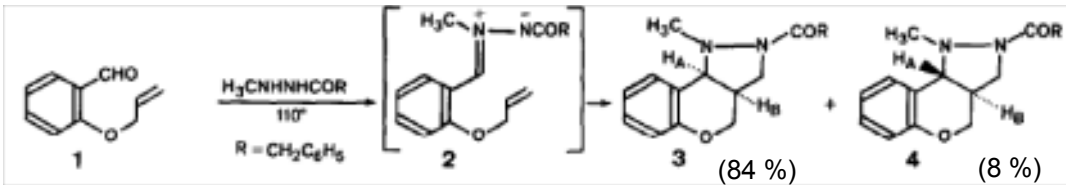




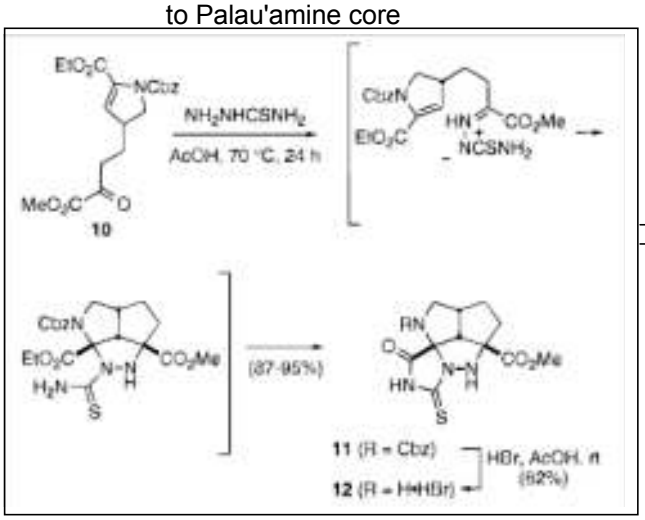


Oppolzer first reported in 1970.(*Tetrahedron Lett*. **1970**, *35,* 3091)

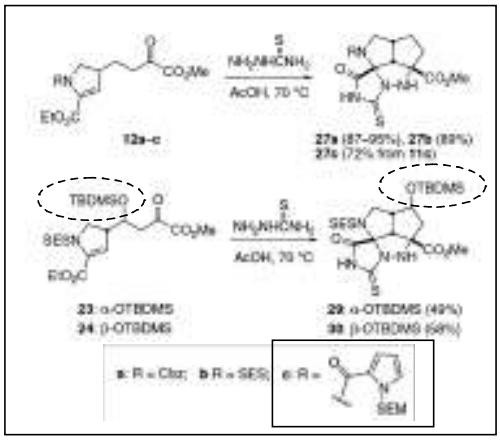




1st report:: application azomethine imine cyclization to Palau'amine core



2nd report : tolerance of FG

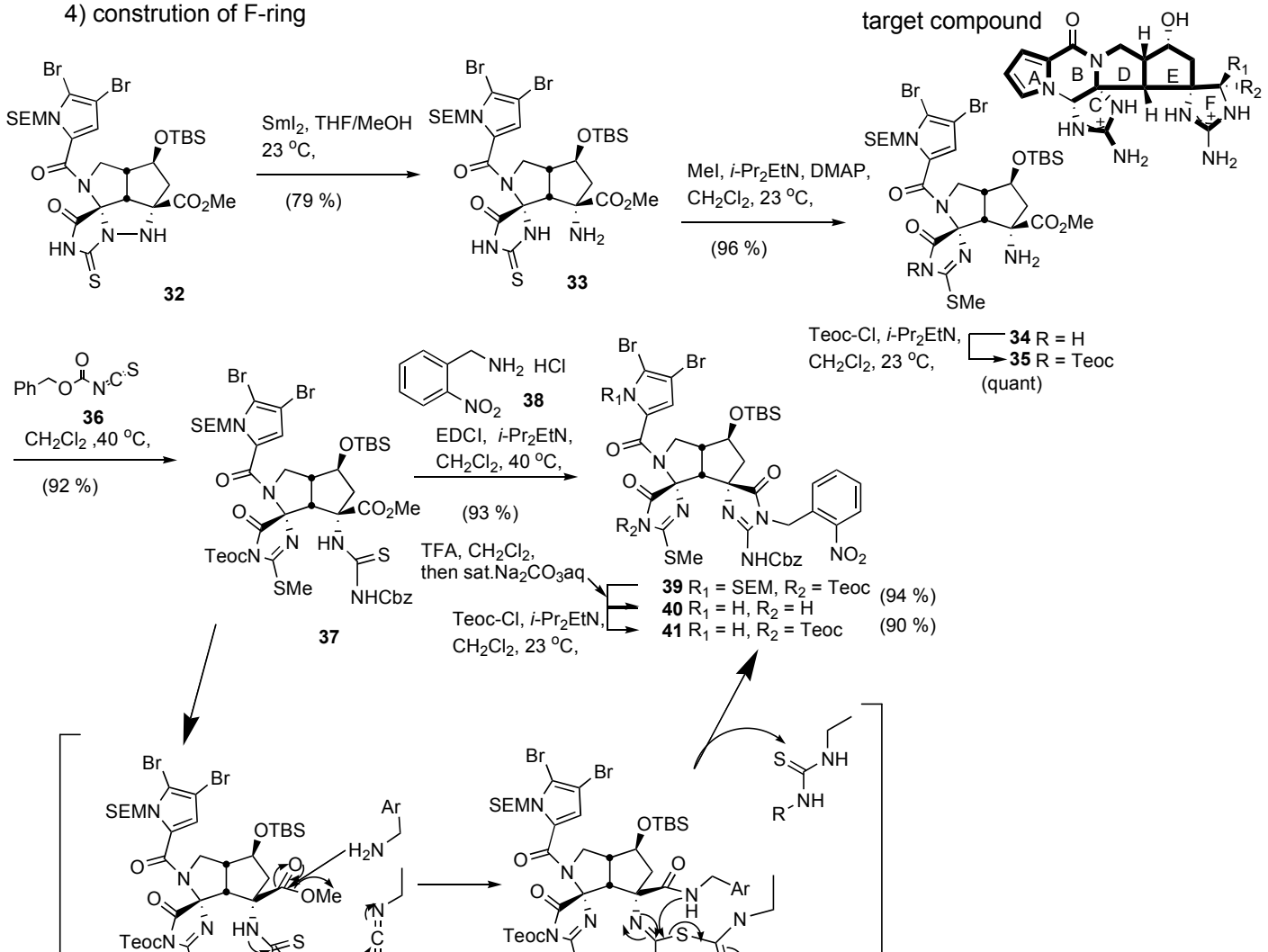


J. Am. Chem. Soc. **1997**, *119*, 7159 (1st)

J. Org. Chem. **2002**, *67*, 7880 (2nd)

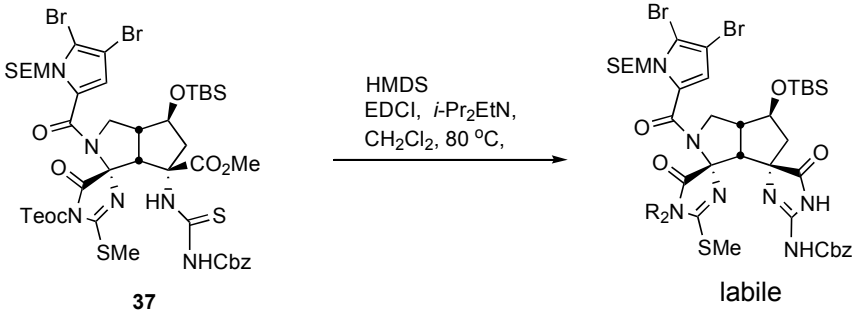
4) constrution of F-ring

target compound



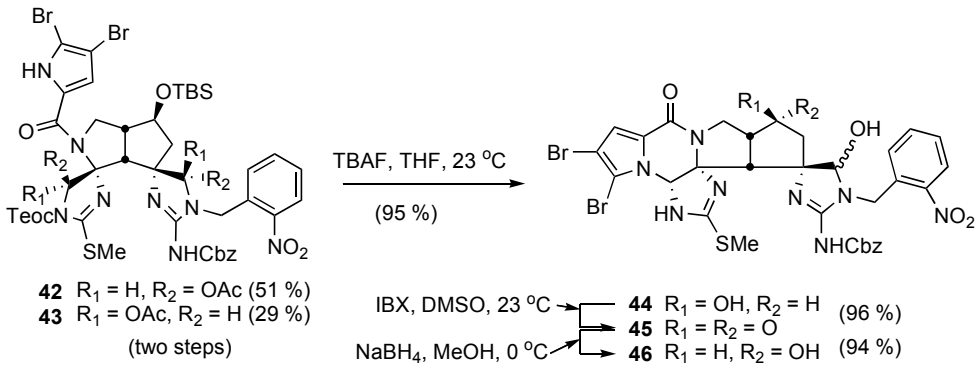
Installation of the 2nd guanidine units

monoprotected

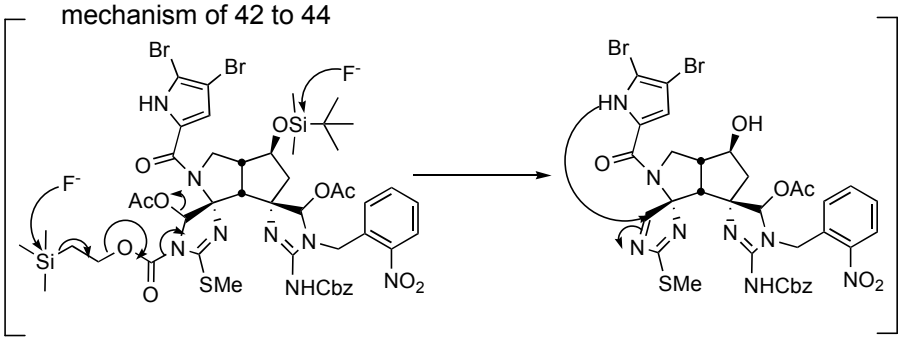


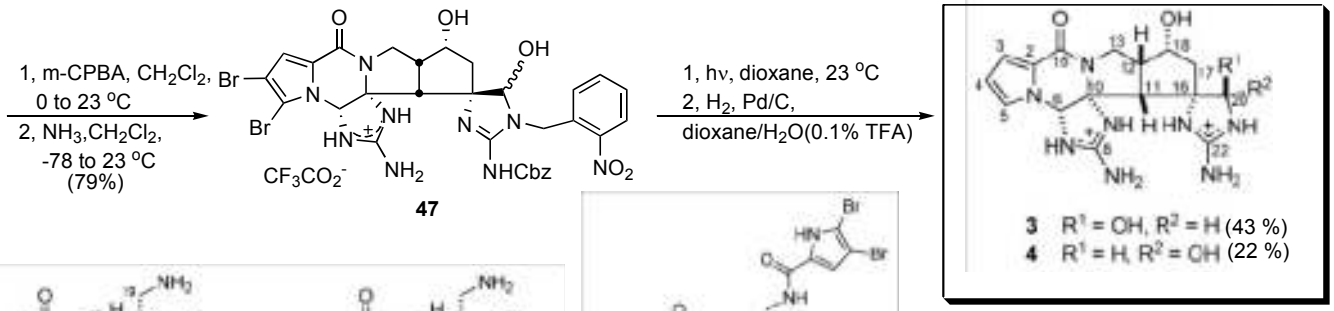
(Y. Ohfune. *Tetrahedron letters,* **2006**, *47,* 1945)

5) Final access to analogs of palau'amine



mechanism of 42 to 44





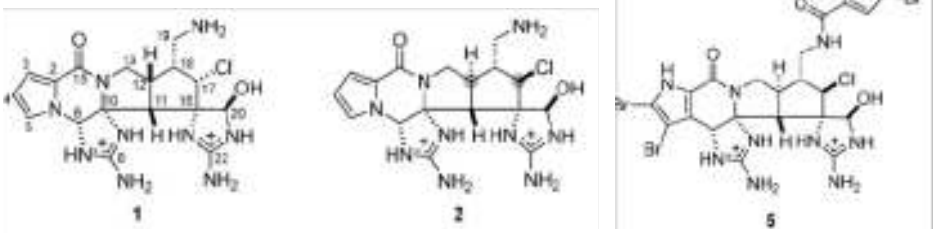


Table 2. Selected Experimental and Calculated Interproton Distances[a]

protons	3[b]	3[c]	4[b]	4[c]	1[c]	*trans*–3[c,d]	*trans*–4[c,d]	5[c]	2[c]
11/12	221	221	228	224	226	304	304	304	303
11/13β	335	342	334	343	407	268	267	270	263
11/18	n.o.	405	n.o.	407	327	253	258	253	277
11/20	270	317	208	221	311	322	264	332	334
12/18	249	240	227	240	221	305	305	303	303
13α/18	313	299	292	297	381	346	345	343	334
13β/18	n.o.	349	n.o.	348	359	251	249	247	252

After volume integration of all-cross peaks in the ROESY spectra,the intensity data were calibrated using the geminal protons at C13 (178pm).Each ROESY spectrum was analyzed separately(linear apprpximation).

Distances obtained from molecular modeling.

2. Synthetic study
ii) Baran's strategy

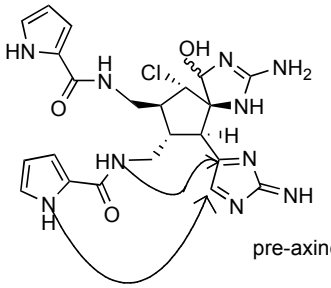
The Pursuit of Palau'amine

Matthias Köck, Achim Grube, Ian B. Seiple, and Phil S. Baran**

Angew. Chem. Int. Ed. **2007**, *46*, 6586.

Baran's strategy is biomimeric

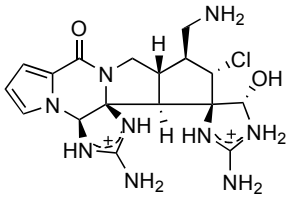
<Proposed biosynthetic route by Baran>



pre-axinellamine(**31**)

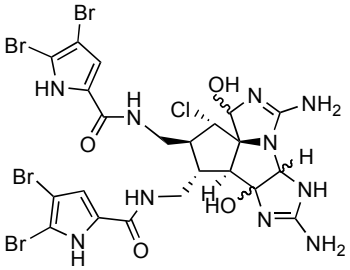
cyclization

amino hydrosis

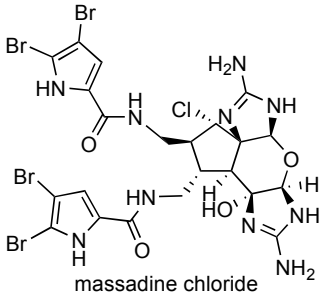


Palau'amine(**2**)
reviced structure

various pyrrole-imidazole alkaloids



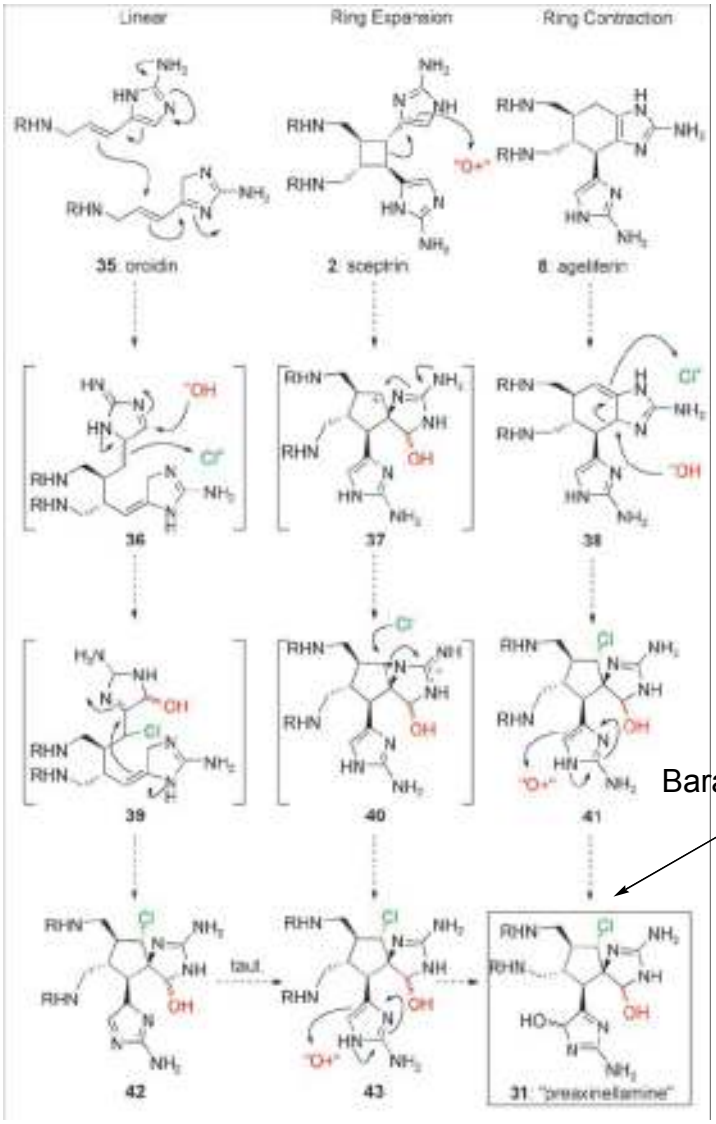
axinellamine



massadine chloride

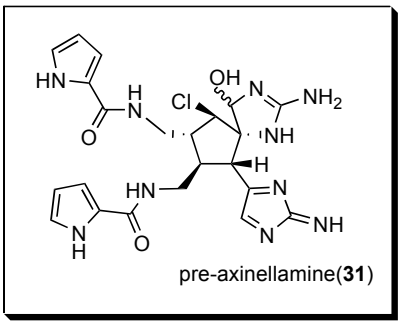
etc.

<possible three ways from natural product (**35, 2, 8**) to pre-axinellamine>



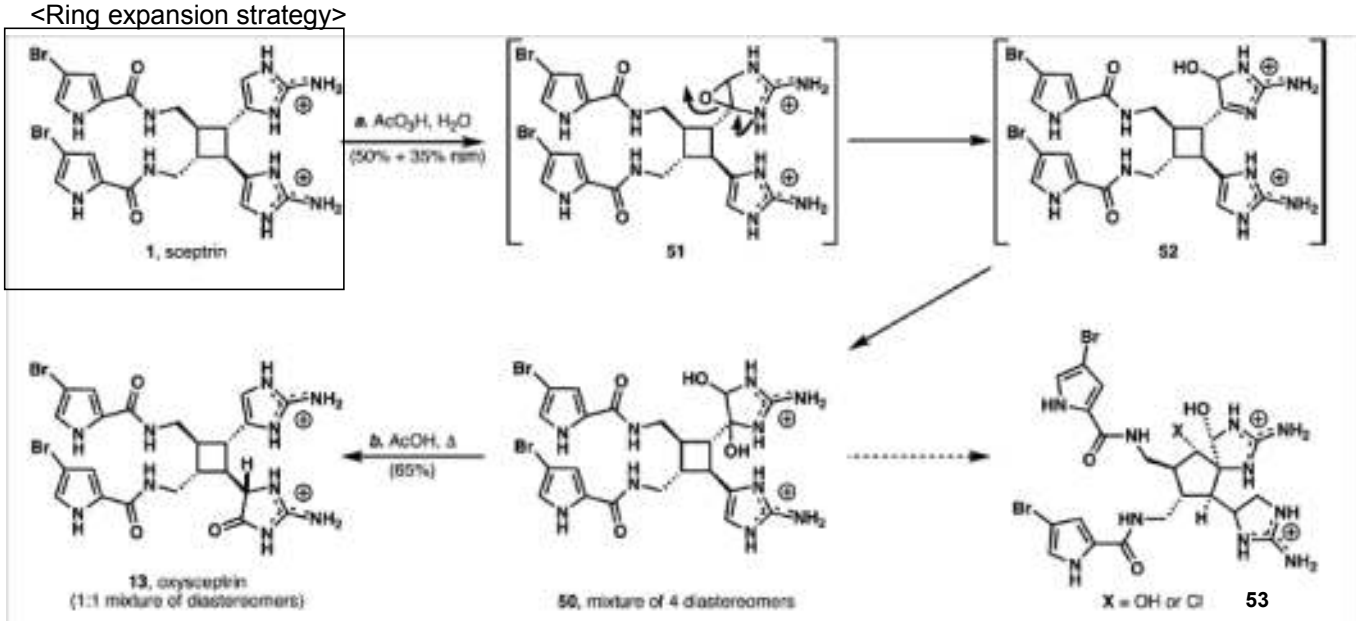
Baran's target

● Synthesis of pre-axinellamine stucture as important intermediate of Palau'amine.

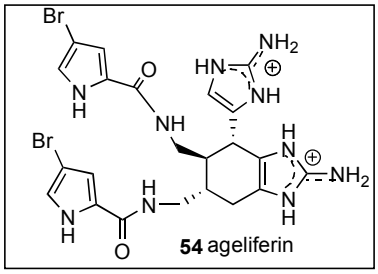


Baran previously reported the synthesis of sceptrin(**1**) and ageliferin(**54**).
P. S. Baran et al.*J. Am. Chem. Soc.* **2007**, *129*, 4762

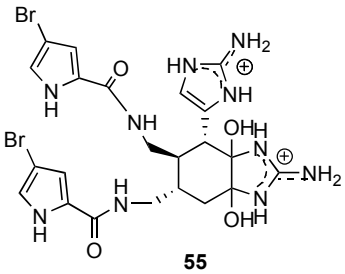
<Ring expansion strategy>

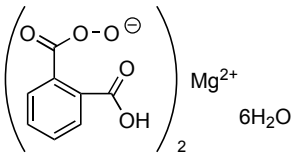


<Ring contruction strategy>



MMPP in H_2O

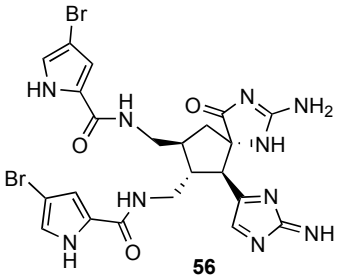




MMPP
higher stability than mCPBA

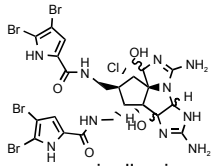
microwave(3 min,120 °C)
5 % $NaHCO_3$ aq / MeOH

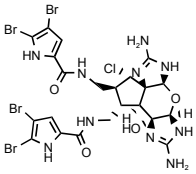
(36% in 2 steps)



epimerization

no report





Delayed installation of trans-azabicyclo[3,3,0]octane Units is difficult.

3. Conclusion

Effects of Revised structure.

non-biomimetic strategy

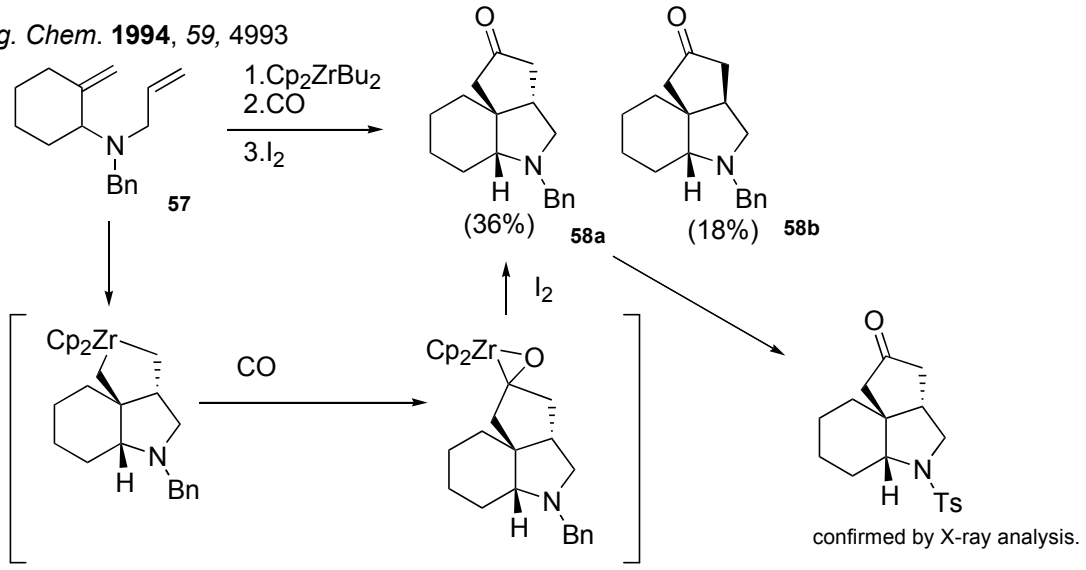
L. E. Overman's comment
Depending upon the synthetic approach being pursued,
this structural revision, if correct, could represent a **significant setback**
for groups engaged in its total synthesis.

biomimetic strategy

P. S. Baran's comment
Most of the strategies reported so far are so flexible that the revised structure of palau'amine will **not be a great setback**.In fact, those research groups that are targeting the axinellamines are now much closer to palau'amine.

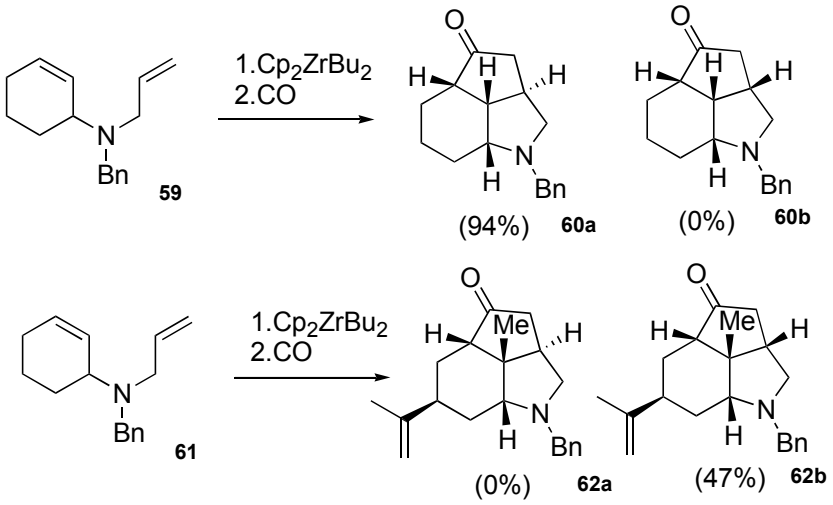
<Most difficult point: Trans-Azabicyclo[3,3,0]octane Units>

Reported example
M. Mori et al. *J. Org. Chem*. **1994**, *59,* 4993



confirmed by X-ray analysis.

Cp_2ZrBu_2 was prepared from Cp_2ZrCl_2 and BuLi .



intermediate of Dendrobine