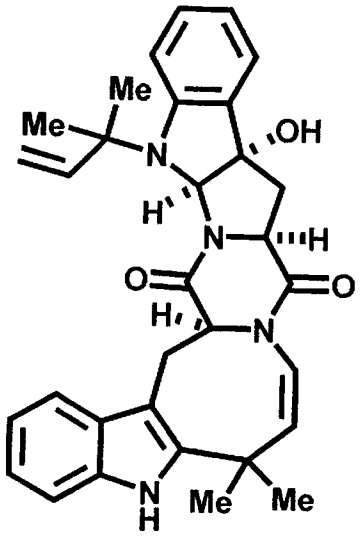
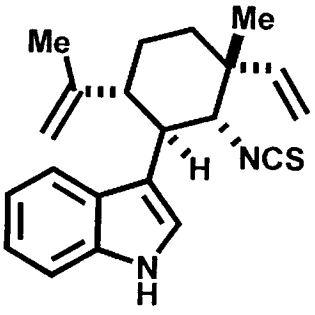
Literature seminar 2004.10.06

Hiroki Shigehisa (D1)

Short synthesis of natural product



Okaramine N



hapalindole Q

Short synthesis of Target compound

biomimetic synthesis (understanding biosynthesis)	+	**Creating new strategy (understanding known chemistry)**

Today's topic

Dr. Baran's recent working

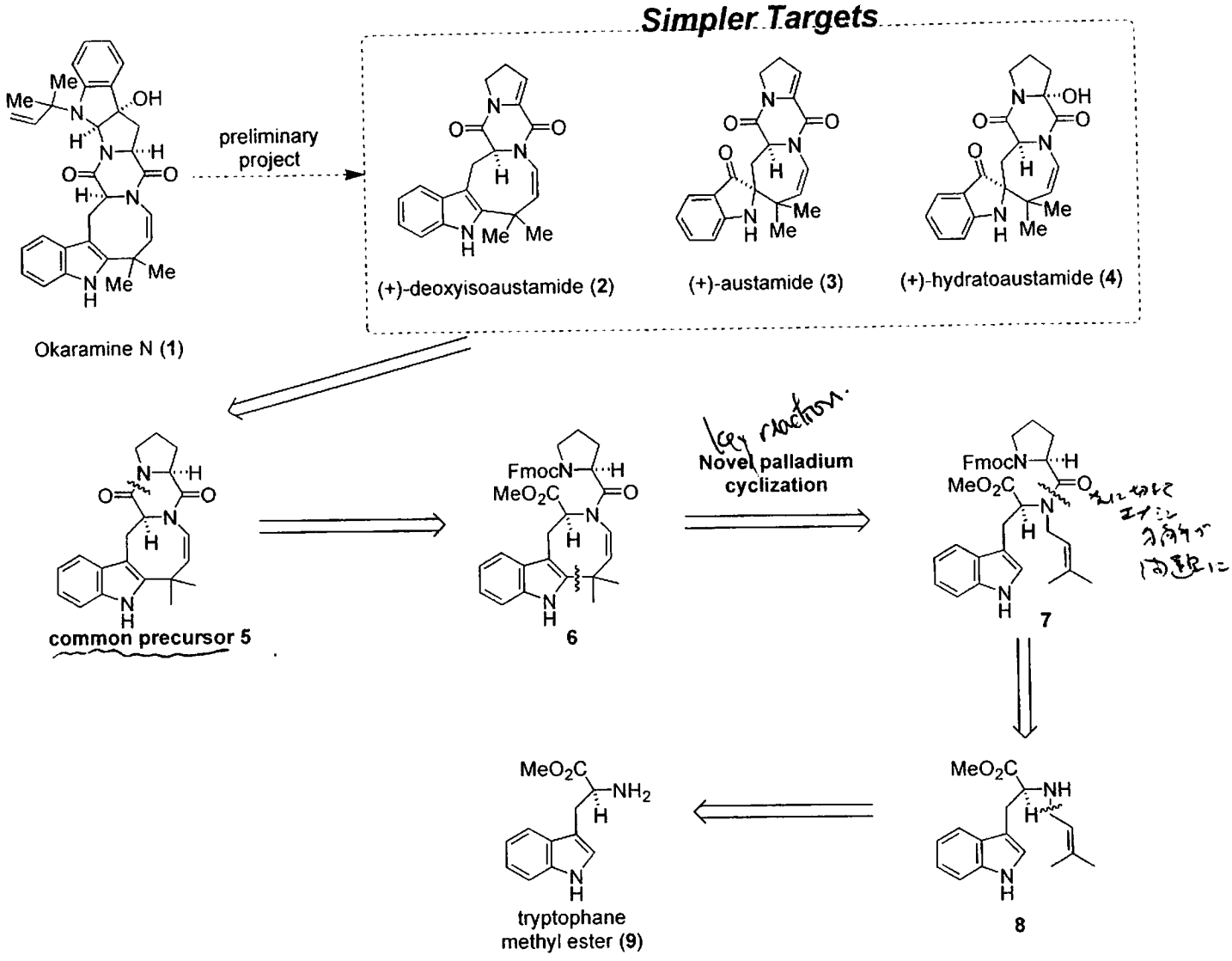
1. **Short** synthetic route to (+)- Austamide, (+)-Deoxyinsoaustamide, and (+)-Hydratoaustamide from a Common Precursor by a Novel Palladium-Mediated Indole Dihydroindoloazocine Cyclization

2. **Short**, Enantioselecitve Total Synthesis of Okaramine N

3. DIrect Coupling of Indoles with Carbonyl Compounds: **Short**, Enantioselecitve, Gram-Scale Synthetic Entry into the Hapalindole and Fischerindole Alkaloid Families

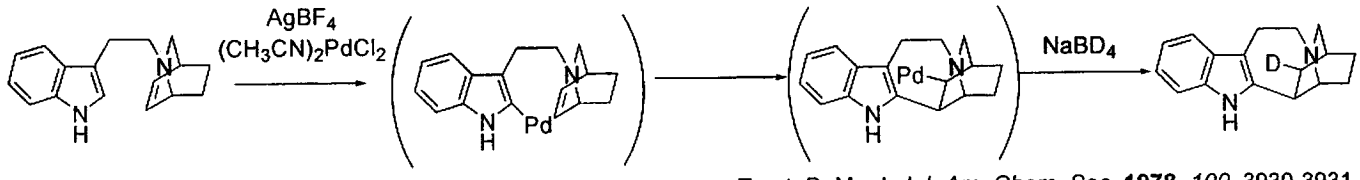
1. Short Synthetic Route to (+)-Austamide, (+)-Deoxyisoaustamide, and (+)-hydroausitamide from a Common Precursor by a Novel Palladium - Mediated Indole - Dihydroindoloazocine Cyclization

(Baran, P. S.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 7904-7905.)

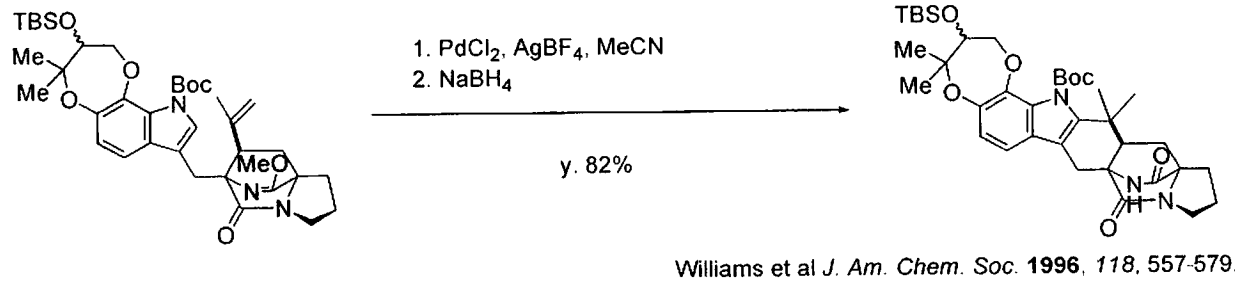


Novel Palladium cyclizatoin 7 → 6

??? **Problematic points 1** : indole C-2 palladation ???

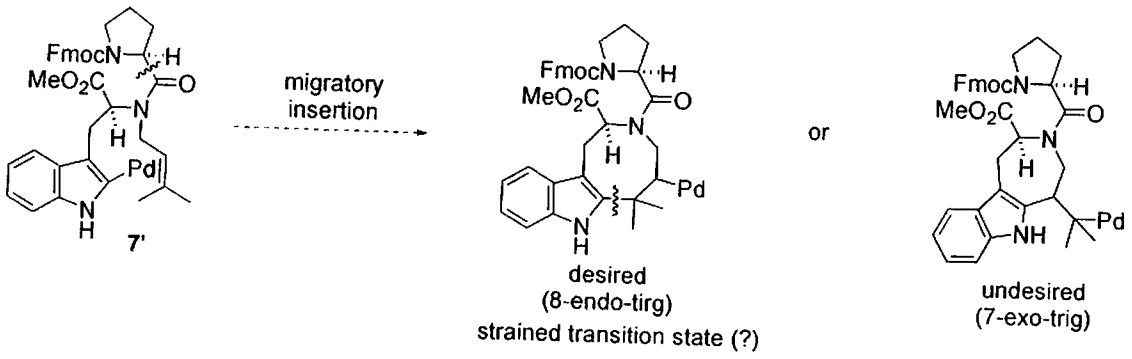


Trost, B. M. et al *J. Am. Chem. Soc.* **1978**, *100*, 3930-3931.

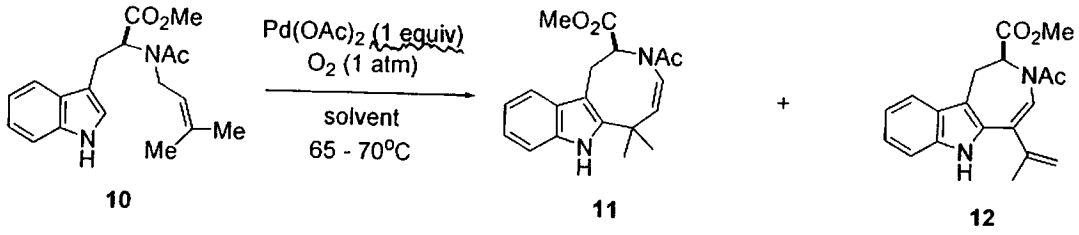


Williams et al *J. Am. Chem. Soc.* **1996**, *118*, 557-579.

??? **Problematic points 2** : 8-endo-trig vs 7-exo-trig ???



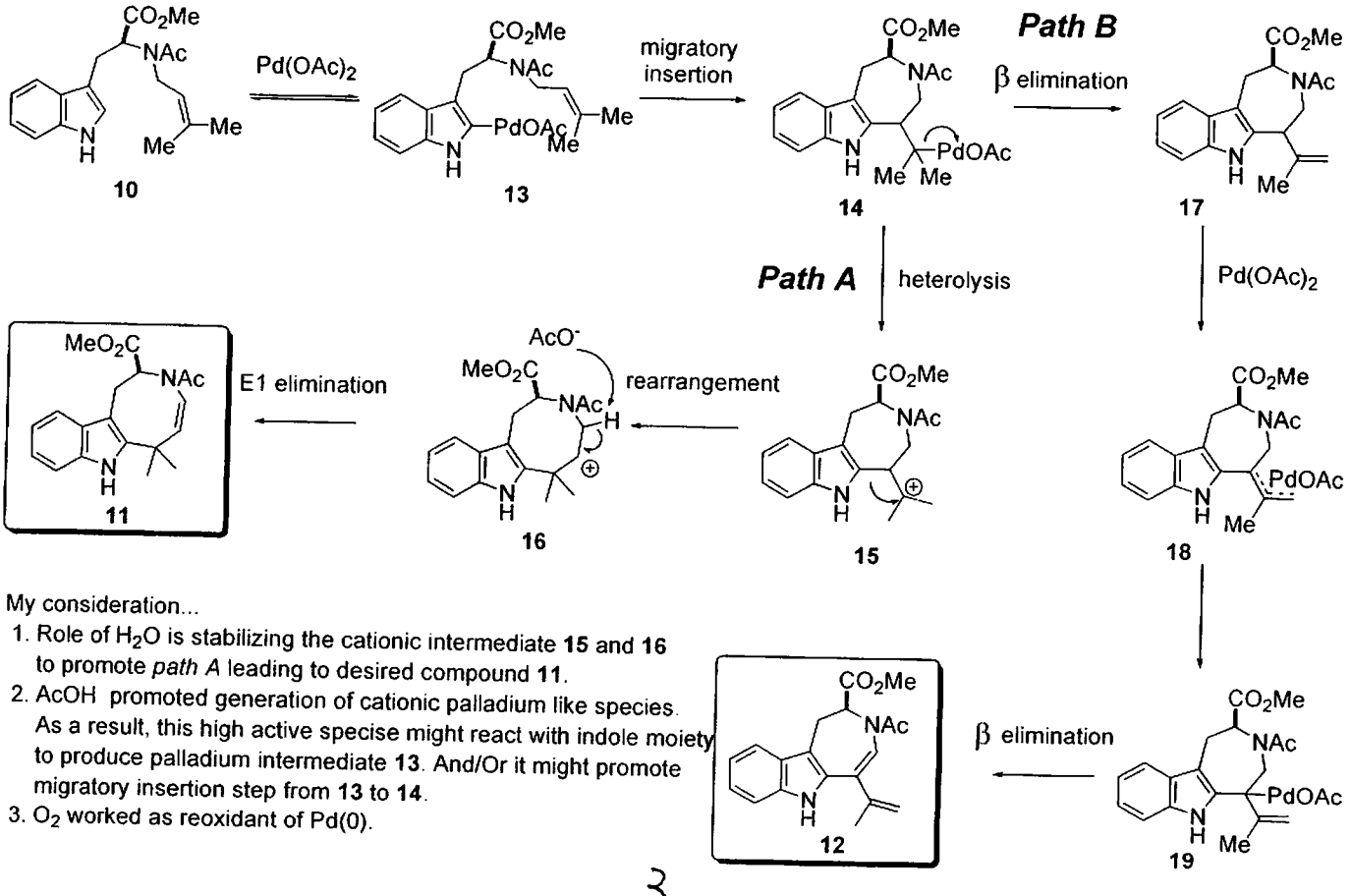
Model Study (supporting infomation)



Entry	Solvent	Ratio **11** : **12**
1	AcOH (reagent grade)	1:4
2	AcOH : H_2O (4:1)	1:1
3	AcOH : H_2O (1:1)	9:1
4	AcOH : H_2O (1:2)	15:1
5	CH_3CN (dry), TFA (2.0 equiv)	1:8
6	H_2O	NR

Both AcOH and H_2O are necessary to get **11** as a major product.

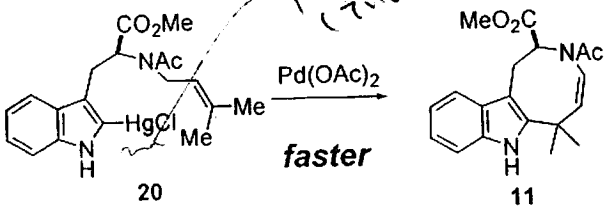
Corey and Baran's proposed mechanism for 11 and 12



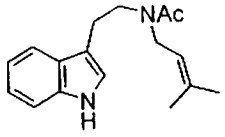
My consideration...

1. Role of H_2O is stabilizing the cationic intermediate **15** and **16** to promote *path A* leading to desired compound **11**.
2. AcOH promoted generation of cationic palladium like species. As a result, this high active specise might react with indole moiety to produce palladium intermediate **13**. And/Or it might promote migratory insertion step from **13** to **14**.
3. O_2 worked as reoxidant of Pd(0).

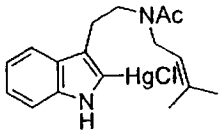
Other experiments



This reaction would proceed through common intermediate generated by transmetallatoin from ~~from~~ Hg to Pd. This result suport their proposed mechanism. The reaction would proceed through palladated species **13**.



cyclized compound



cyclized compound

Their comment : Coordinaion by methoxycarbonyl group with Pd(II) both in indole palladation and in the internal Heck reaction is neccesary.

Natural products synthesis

3 ⟶ (4) ⟶ (5)

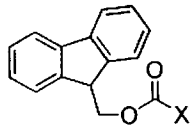
one pot reductive amination - amide formation process

(5) ⟶ 6

Novel palladium cyclization

6 ⟶ 7

Deprotection of Fmoc



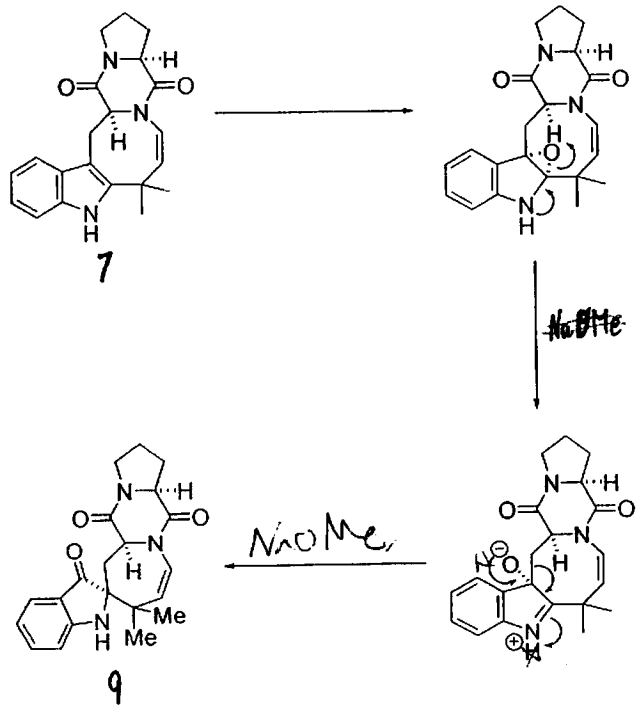
7 ⟶ 8

9 ⟶ 10

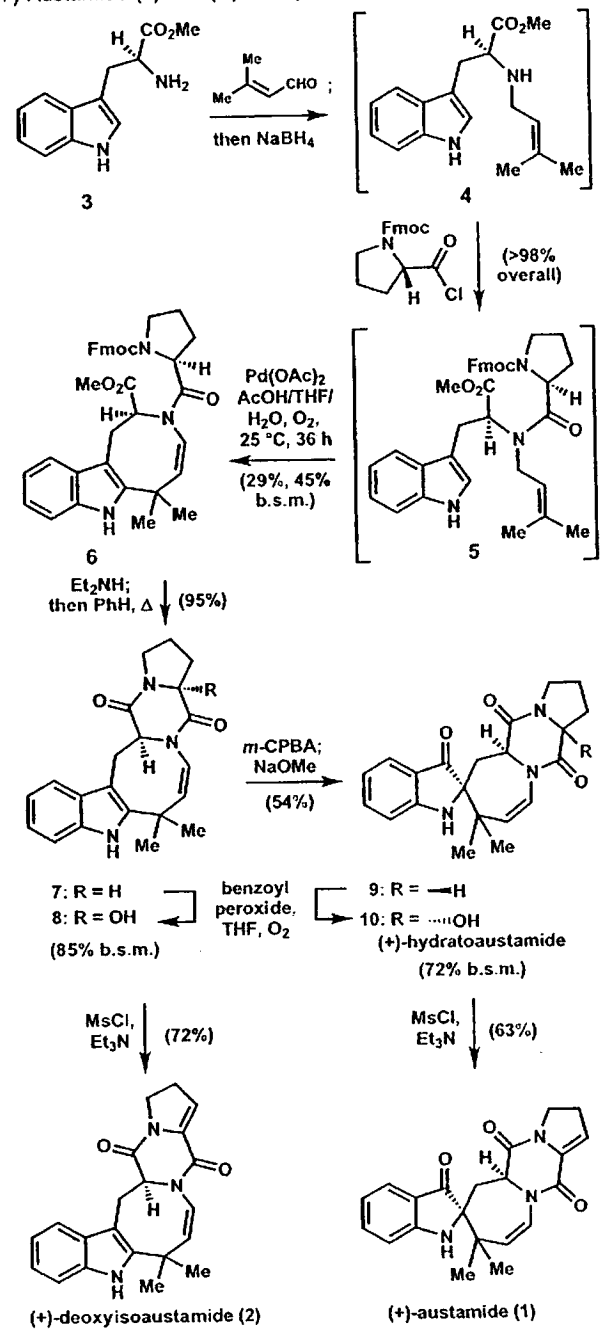
Based on model studey, O_2 was coming from sterically less hinderd face. (Biommetic process??)

7 ⟶ 9 (Biommetic process??)

Epoxidatoin of the 2,3-bond of the indole subunit with subsequent C-O cleavage to form a 3-hydroxy indole then converted diastreoselectively to the spirocyclic oxiindole



Scheme 1. First Enantioselective Total Syntheses of (+)-Austamide (**1**) and (+)-Deoxyisoaustamide (**2**)



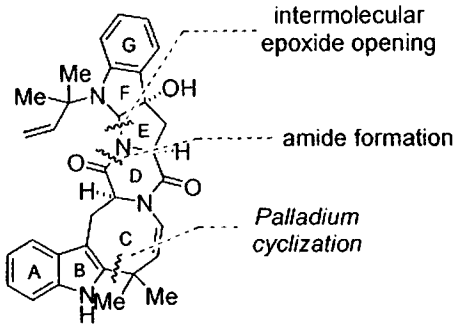
2. Short, Enantioselective Total Synthesis of Okaramine N

(Baran, P. S.; Guerrero, C. A.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 5628-5629.)

they said...

We were surprised and repeatedly humbled by the large number of completely unforeseen roadblocks. Many key transformations in alternateve route to **1**, which a priori seemed likely to succeed, failed completely. In many respects, the development of the synthesis of **1**, which is outlined in Scheme, was similar to finding a way up a vertical cliff that offers just a limited number of small cracks and handhold.

Synthetic strategy



Okaramine N (**1**)

8 ⟶ 9

propargyl amine formation (Murahashi method)

Synthesis of F-G ring subunit

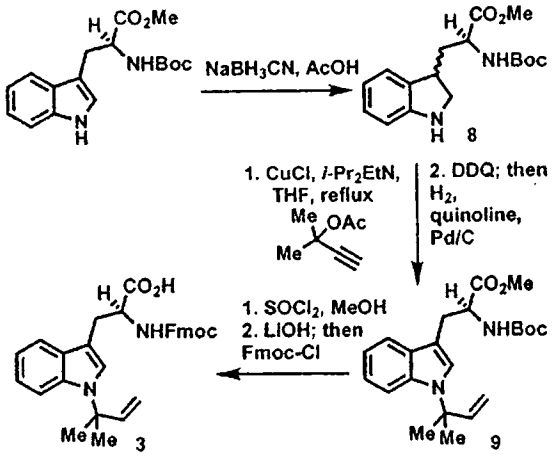
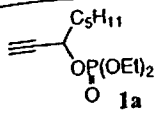
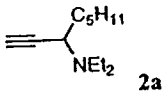
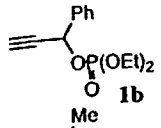
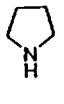
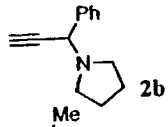
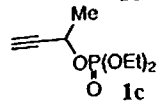
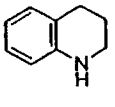
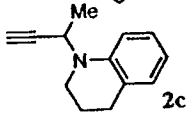
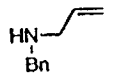
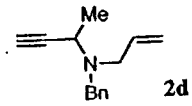
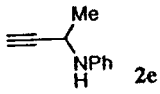
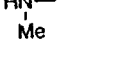
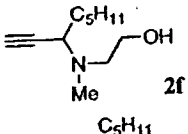
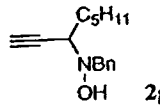
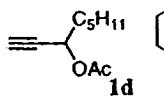
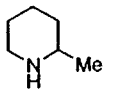
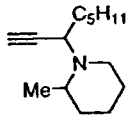
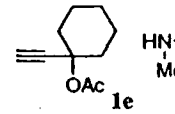
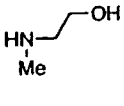
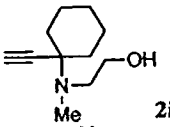
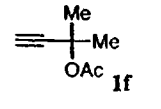
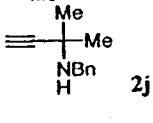


Table 1. Copper-Catalyzed Amination of Propargyl Phosphates[a]

entry	propargyl phosphate	amine	propargylamine	yield,[b] %
1	 **1a**	$HNEt_2$	 **2a**	91
2	 **1b**		 **2b**	75
3	 **1c**		 **2c**	85
4	**1c**		 **2d**	60
5	**1c**	H_2NPh	 **2e**	85
6	**1a**		 **2f**	84
7	**1a**		 **2g**	95

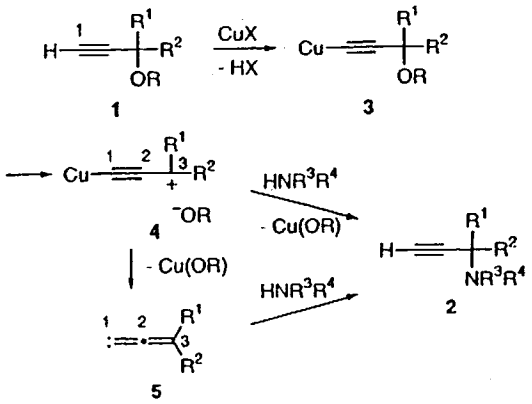
[a] The reaction of propargyl phosphates with amines (2 equiv) was performed in the presence of CuCl (1 mol %) in THF at 50 °C for 2 h. [b] Isolated yield.

Table 2. Copper-Catalyzed Amination of Propargyl Acetates[a]

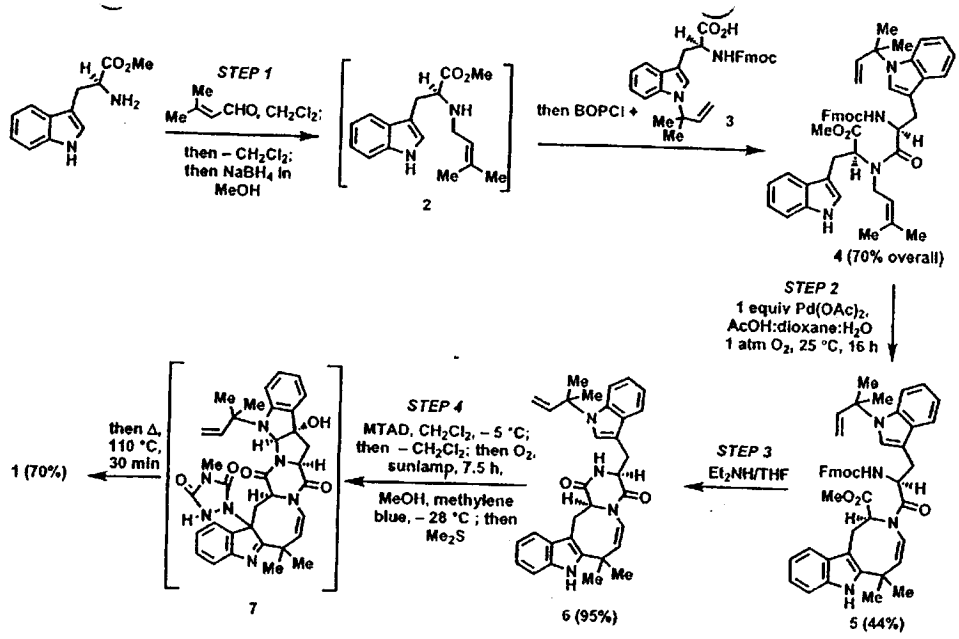
entry	propargyl acetate	amine	propargylamine	yield,[b] %
1	 **1d**		 **2h**	72
2	 **1e**		 **2i**	80
3	 **1f**	H_2NBn	 **2j**	62

[a] The reaction of propargyl acetates with amines (2 equiv) was performed in the presence of CuCl (5 mol %) in THF at reflux for 2 h. [b] Isolated yield.

Scheme 1

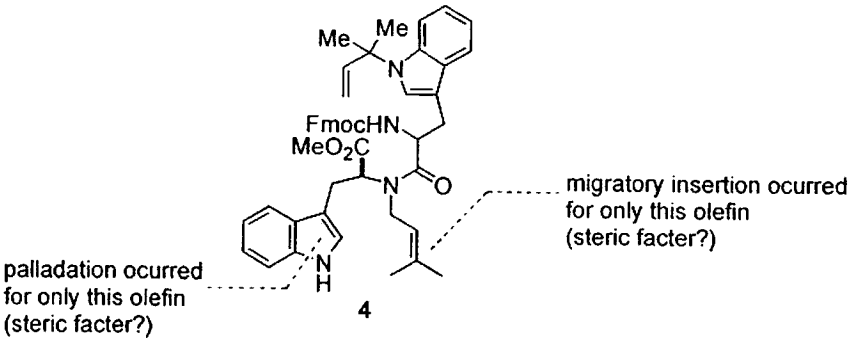


Scheme 1. Enantioselec Synthesis of Okaramine N

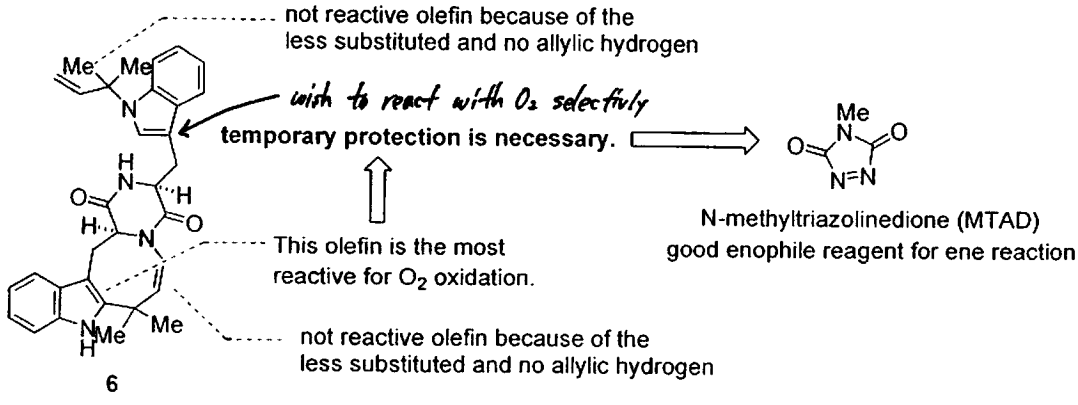


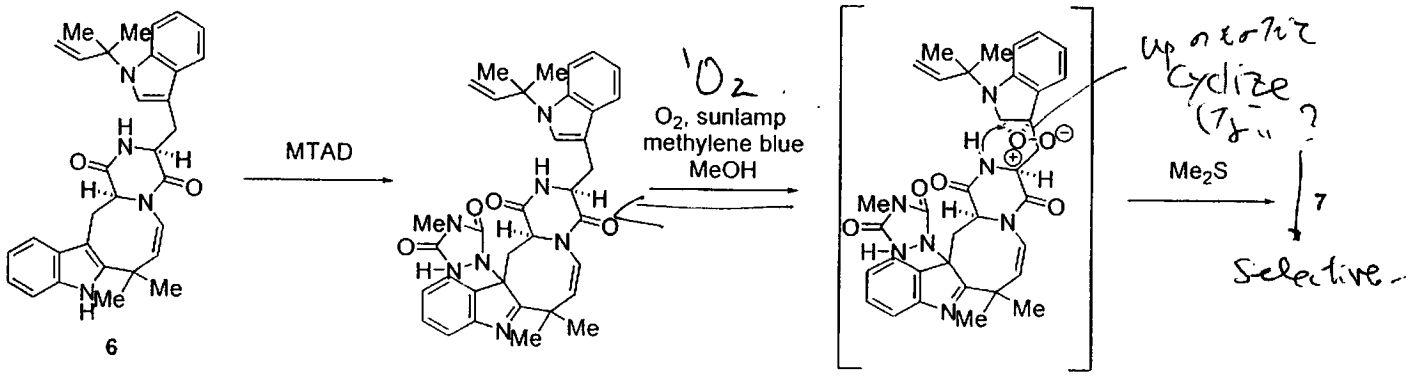
4 ⟶ 5

only the N-substituted subunit appeared to react, and only eight membered ring formation was observed

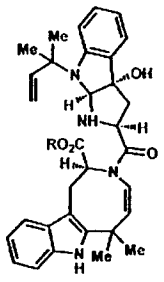


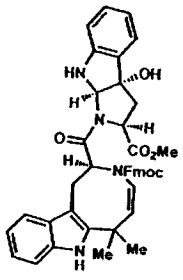
6 ⟶ (7) ⟶ 1



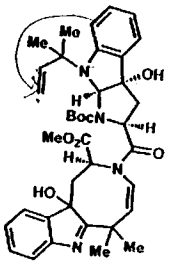


failed examples





never cyclized

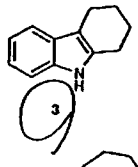
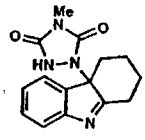
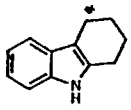
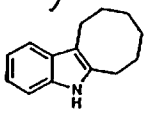
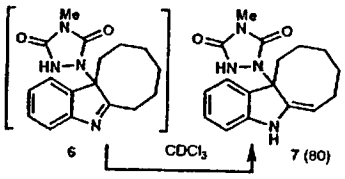
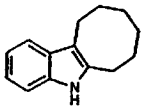
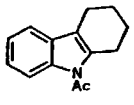
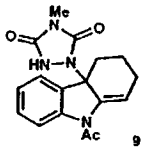
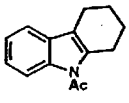
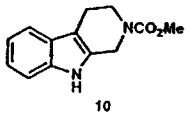
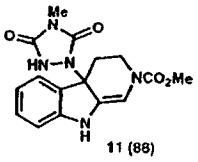
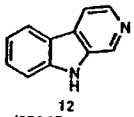
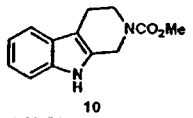
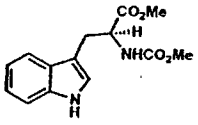
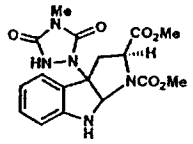
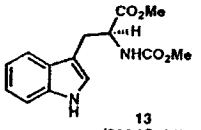
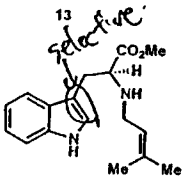
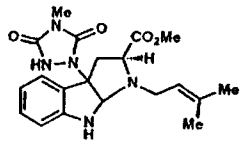
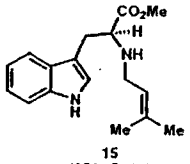
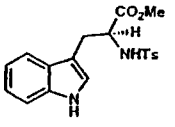
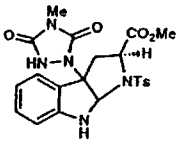
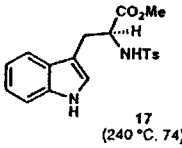
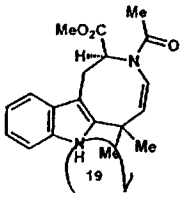
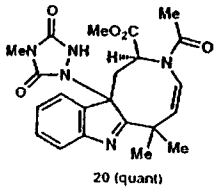
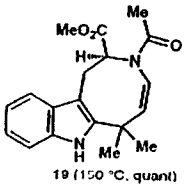


→ Claisen rearrangement

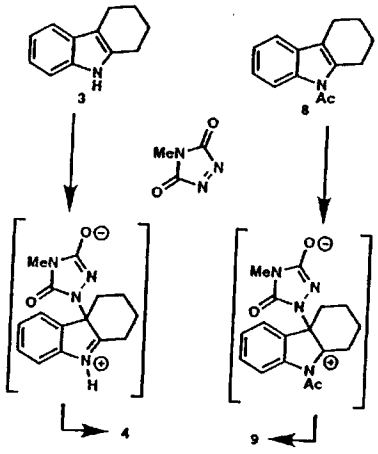
3. The First Method for Protection - Deprotection of the Indole 2,3 - π Bond

(Baran, P. S.; Guerrero, C. A.; Corey, E. J. *Org. Lett.* **2003**, *5*, 1999-2001.)

Ene Reaction of Indoles with MIAD and Retro-ene Deprotection

substrate	ene product (yield %)	retro-ene product (temp, yield %)
 3	 4 (quant)	 3 (120 °C, quant)
 5	 6 $\xrightarrow{CDCl_3}$ 7 (80)	 5 (280 °C, 85)
 8	 9 (84)	 8 (250 °C, 90)
 10	 11 (88)	 12 (250 °C, *ca.* 90)  10 (cat. $MeSO_3H$, 25 °C, 8 h, 68)
	 14 (62, 1:1 mixture of diastereomers)	 13 (280 °C, 90)
 15	 16 (80, 1:1 mixture of diastereomers)	 15 (250 °C, 65)
 17	 18 (58, 2:1 mixture of diastereomers)	 17 (240 °C, 74)
 19	 20 (quant)	 19 (150 °C, quant)

Mechanism



The reaction is accelerated in MeOH.

In the case of 8

CH_2Cl_2 → 4h

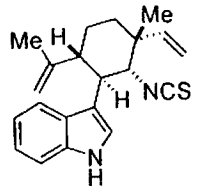
MeOH → 10 min

However ...

In the case of Okaramine N's protect MeOH gave the bad selectivity.

4. Direct Coupling of Indoles with Carbonyl Comopunds : Short, Enantioselective, Gram-Scale Synthetic Entry into the Hapalindole and Fishcherindole Alkaloid Families

(Baran, P. S.; Jeremy M. Richter. *J. Am. Chem. Soc.* **2004**, *126*, 7450-7451.)



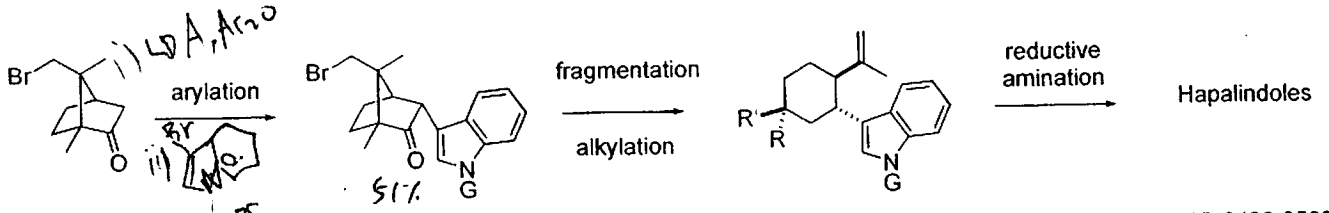
(+)-Hapalindole Q

anti-algal
anti-mycoticactivity

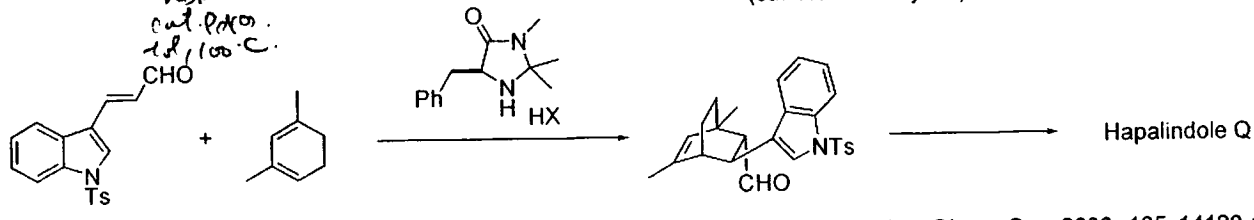
⇩

inhibition of RNA polymerase

Previous synthetic examples

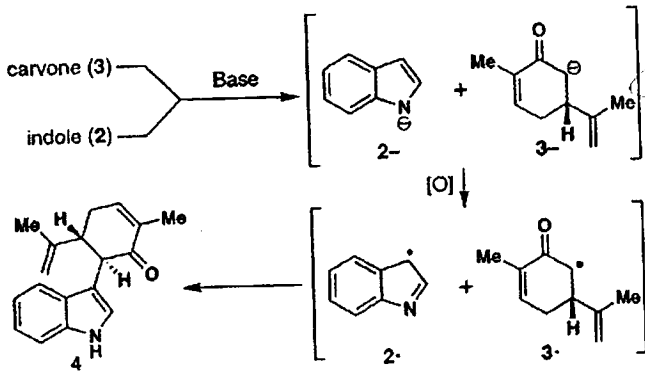


Albizati et al *J. Am. Chem. Soc.* **1993**, *115*, 3499-3502.
(ca. 4% overall yield)



Kerr et al *J. Am. Chem. Soc.* **2003**, *125*, 14120-14125.
(ca. 1.0% overall yield)

Baran's concept (figure 1)



dimerization of enolate ⟶ known

heterocoupling ⟶ little and low yield

indole dimer was not observed.

Table 1. Selected Optimization Results of **2** + **3** → **4**

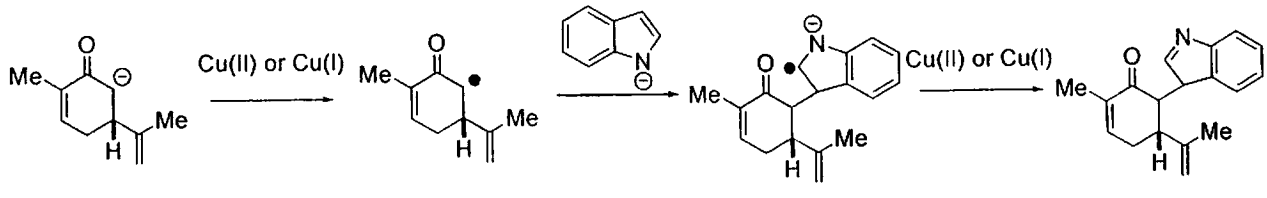
indole (2) + carvone (3) — THF, Base, then [O] → **4**
[O] = $FeCl_3$/DMF (Fe) or Copper(II)2-ethylhexanoate (Cu)

Entry	Conditions	Yield (%)[a]
1	2 (1.0 eq), 3 (3.0 eq), LDA (4.0 eq), Fe (4.0 eq), –78 to 23 °C	*ca* 15
2	2 (1.0 eq), 3 (3.0 eq), LDA (4.0 eq), Cu (4.0 eq), –78 to 23 °C	24
3	2 (1.0 eq), 3 (1.0 eq), LDA (2.0 eq), Cu (2.0 eq), –78 to 0 °C	24
4	2 (3.0 eq), 3 (1.0 eq), LDA (4.0 eq), Cu (4.0 eq), –78 to 0 °C	32
5	2 (2.0 eq), 3 (1.0 eq), LHMDS (3.0 eq), Cu (1.5 eq), –78 °C	53 (70)[b]

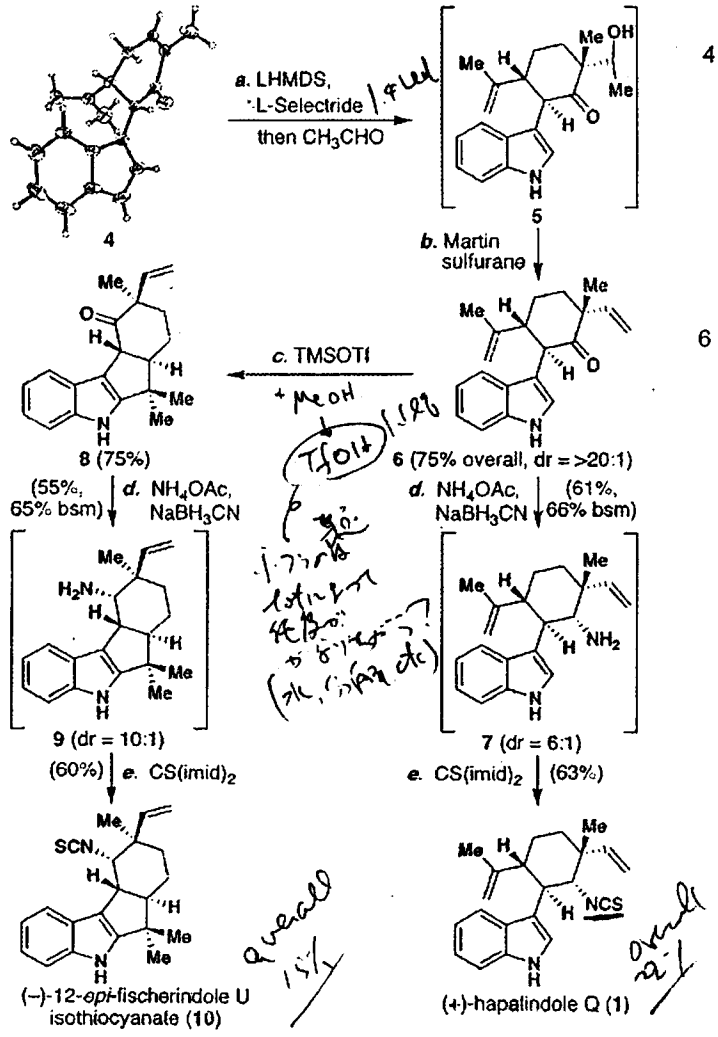
[a] Isolated yield after chromatography. [b] Yield based on recovered sm.

⇩

Real mechanism of this dimerization can be different from that shown like figure 1.

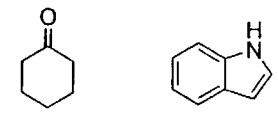


Scheme 1. Enantioselective Total Syntheses of (+)-1 and (−)-10[a]



[a] Reagents and conditions: (a) LHMDS (1.5 equiv), THF, −78 °C, 20 min then L-Selectride (1.05 equiv), 1 h, then CH_3CHO (6.0 equiv), −78→23 °C, 2 h; (b) Martin sulfurane (1.1 equiv), $CHCl_3$, 10 min, 75% overall; (c) TMSOTf (3.0 equiv), MeOH (1.1 equiv), CH_2Cl_2, 0 °C, 1 h, 75% bsm; (d) $NaBH_3CN$ (10 equiv), NH_4OAc (40 equiv), MeOH, THF, 150 °C, 2 min, 61% (7); for 9: same reagents, 23 °C, 48 h, 55%; (e) $CS(imid)_2$ (1.1 equiv), CH_2Cl_2, 0→23 °C, 3 h, 63% (1), 60% (10).

4 ⟶ 5



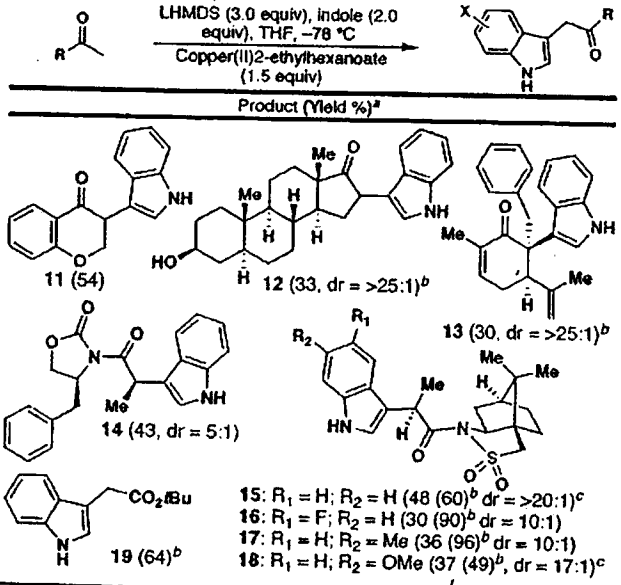
pKa=25.8 (in DMSO) pKa=20.95

LHMDS
for deprotonation of indole
L-selectride
1,4-reduction
CH_3CHO
from α side because of steric repulsion with indole ring

6 ⟶ 7

microwave enhanced reductive amination
@ albizati synthesis
in MeOH,THF, 25°C, 7 days y. 62% for 2 steps

Table 2. Preparation of α-Indole Carbonyl Compounds



[a] Isolated yield after chromatography. [b] Yield based on recovered sm. [c] LDA used.