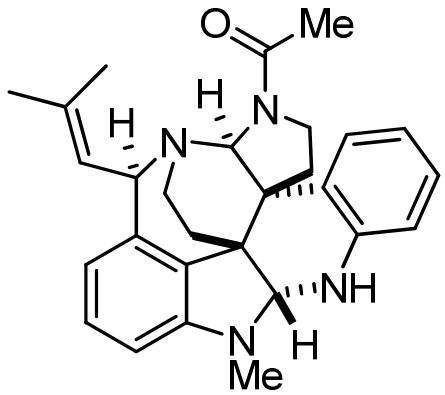
Total Synthesis and Absolute Stereochemical Assignment of (–)-Communesin F

Zhiwei Zuo, Weiqing Xie, Dawei Ma*

Shanghai Institute of Organic Chemistry, Shanghai, China

J. Am. Chem. Soc. **2010**, *132*, 13226-13228.



Marie-Céline Frantz

Wipf Group - Current Literature

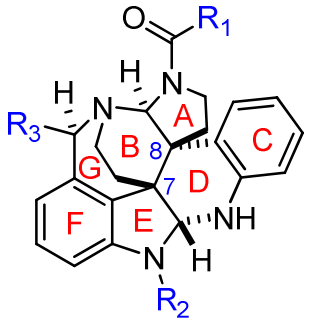
September 25, 2010

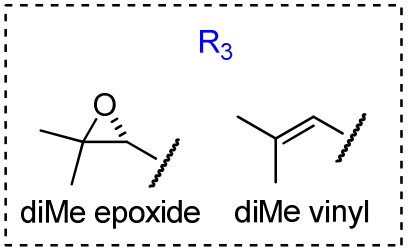
Penicillium

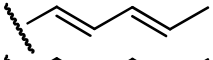
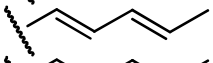
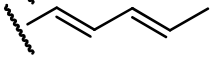
Communesin Familly

Marine alga *Enteromorpha Intestinalis*

- Emerging class of metabolites isolated from different marine and terrestrial species of the genus *Penicillium*.
- Communesins A and B first identified in 1993 by Numata from a strain of *Penicillium* sp. isolated from the marine algae *Enteromorpha intestinalis*.
- 8 members disclosed to date (communesins A-H).
- Indole polycyclic alkaloids with:
  - 2 vicinal quaternary centers at C7/8
  - 2 aminal moieties.
- Biological activity:
  - moderate antiproliferative activity against several human leukemia cell lines
  - active against brine shrimps
  - antihelmintic activity
  - insecticidal activity against silkworms
  - microfilaments disruption.



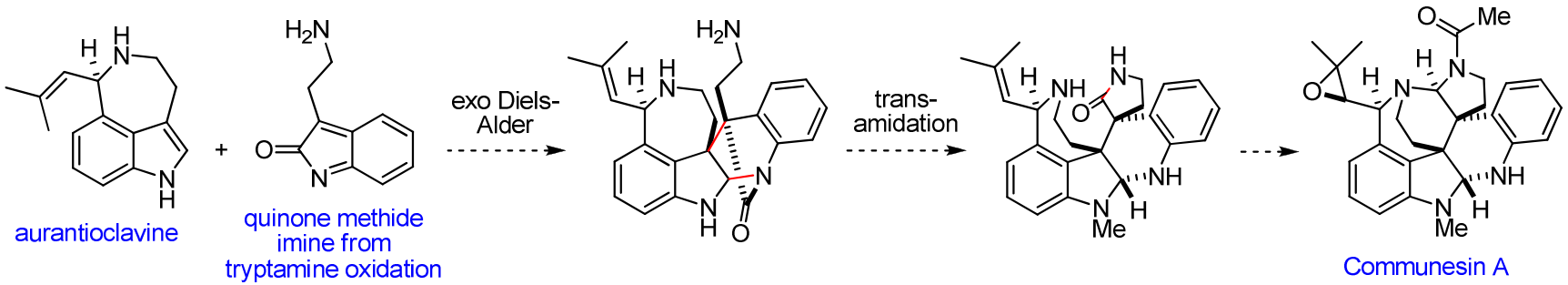


	R_1	R_2	R_3
Communesin A	Me	Me	diMe epoxide
Communesin B		Me	diMe epoxide
Communesin C		H	diMe epoxide
Communesin D		CHO	diMe epoxide
Communesin E	Me	H	diMe epoxide
Communesin F	Me	Me	diMe vinyl
Communesin G	Et	Me	diMe epoxide
Communesin H	*n*-Pr	Me	diMe epoxide

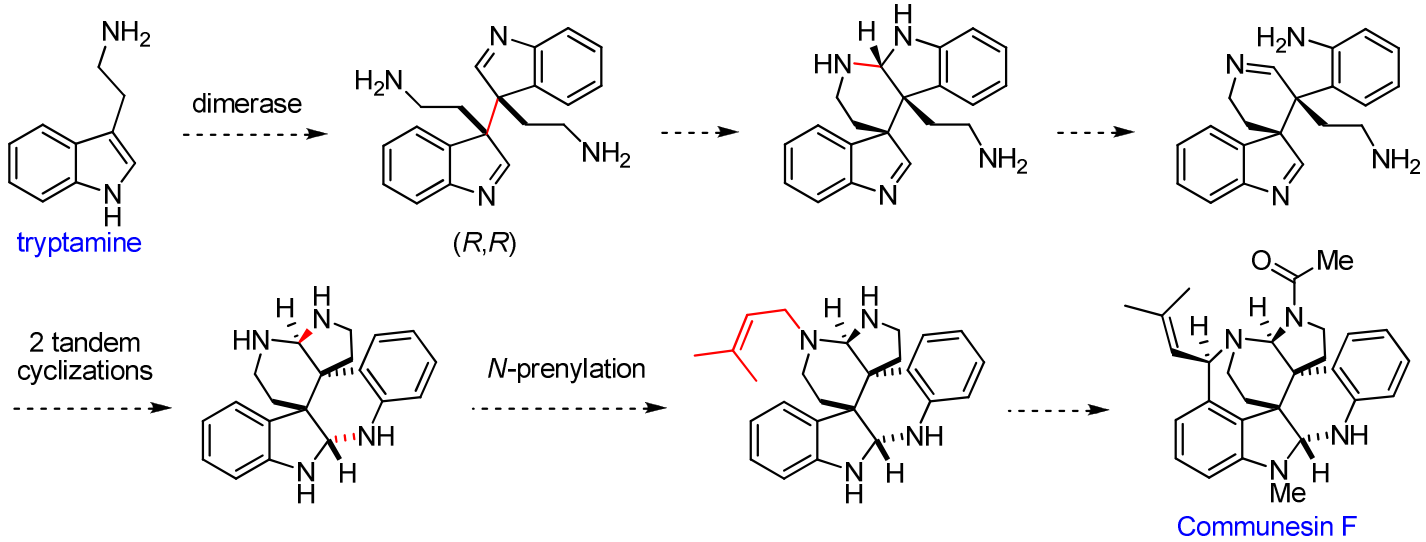
Numata, A.; Takahashi, C.; Ito, Y.; Takada, T.; Kawai, K.; Usami, Y.; Matsumura, E.; Imachi, M.; Ito, T.; Hasegawa, T. *Tetrahedron Lett.* **1993**, *34*, 2355. Jadulco, R.; Edrada, R. A.; Ebel, R.; Berg, A.; Schauman, K.; Wray, V.; Steube, K.; Proksch, P. *J. Nat. Prod.* **2004**, *67*, 78. Hayashi, H.; Matsumoto, H.; Akiyama, K. *Biosci., Biotechnol., Biochem.* **2004**, *68*, 753. Dalsgaard, P. W.; Blunt, J. W.; Munro, M. H. G.; Frisvad, J. C.; Christophersen, C. *J. Nat. Prod.* **2005**, *68*, 258. Kerzaon, I.; Pouchus, Y. F.; Monteau, F.; Le Bizec, B.; Nourrisson, M. R.; Biard, J. F.; Grovel, O. *Rapid Commun. Mass Spectrom.* **2009**, *23*, 3928.

Communesins: Proposed Biosynthetic Pathways

- Stoltz and co-workers (2003)



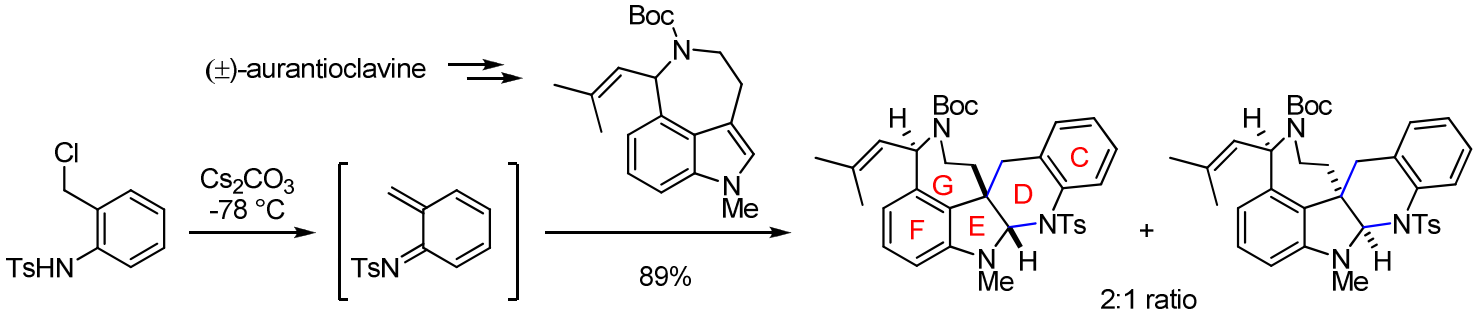
- Mantle and co-workers (2006), further developed by Stoltz and May (2006)



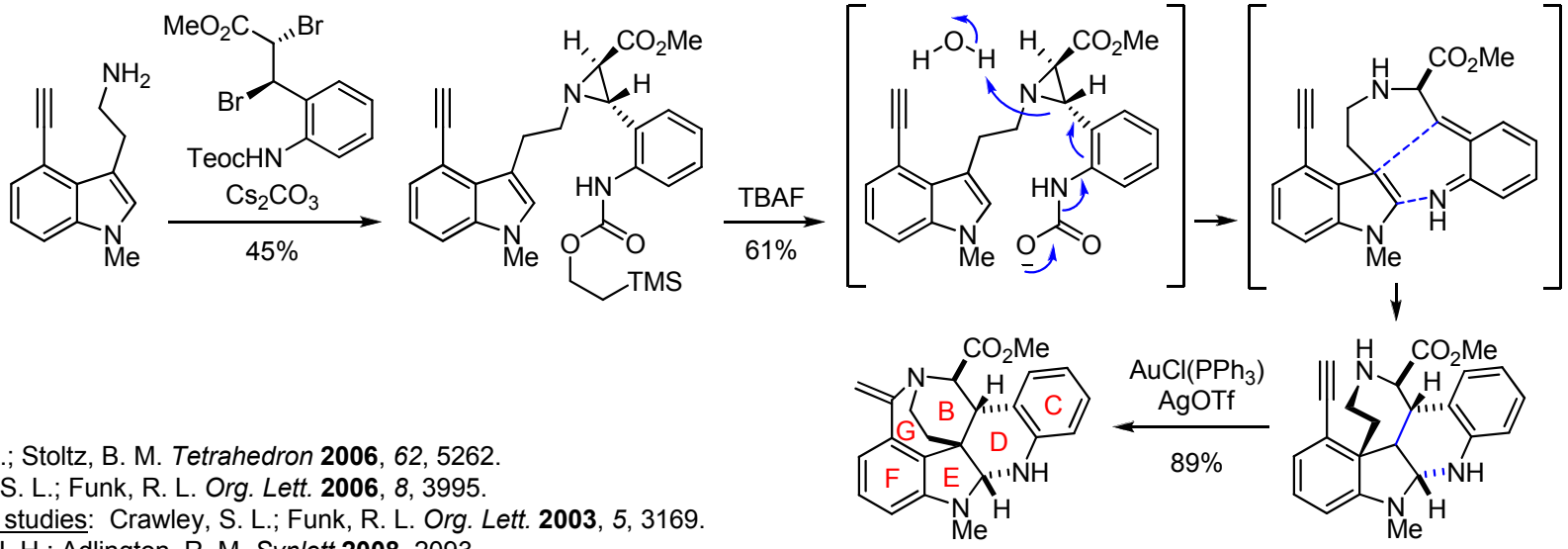
May, J. A.; Zeidan, R. K.; Stoltz, B. M. *Tetrahedron Lett.* **2003**, *44*, 1203. Wigley, L. J.; Mantle, P. G.; Perry, D. A. *Phytochemistry* **2006**, *67*, 561. May, J. A.; Stoltz, B. M. *Tetrahedron* **2006**, *62*, 5262.
For a short review: Siengalewicz, P.; Gaich, T.; Mulzer, J. *Angew. Chem. Int. Ed.* **2008**, *47*, 8170.

Communesins: Synthetic Studies

- Stoltz and May (2006): Biomimetic model study of inverse-demand Diels-Alder

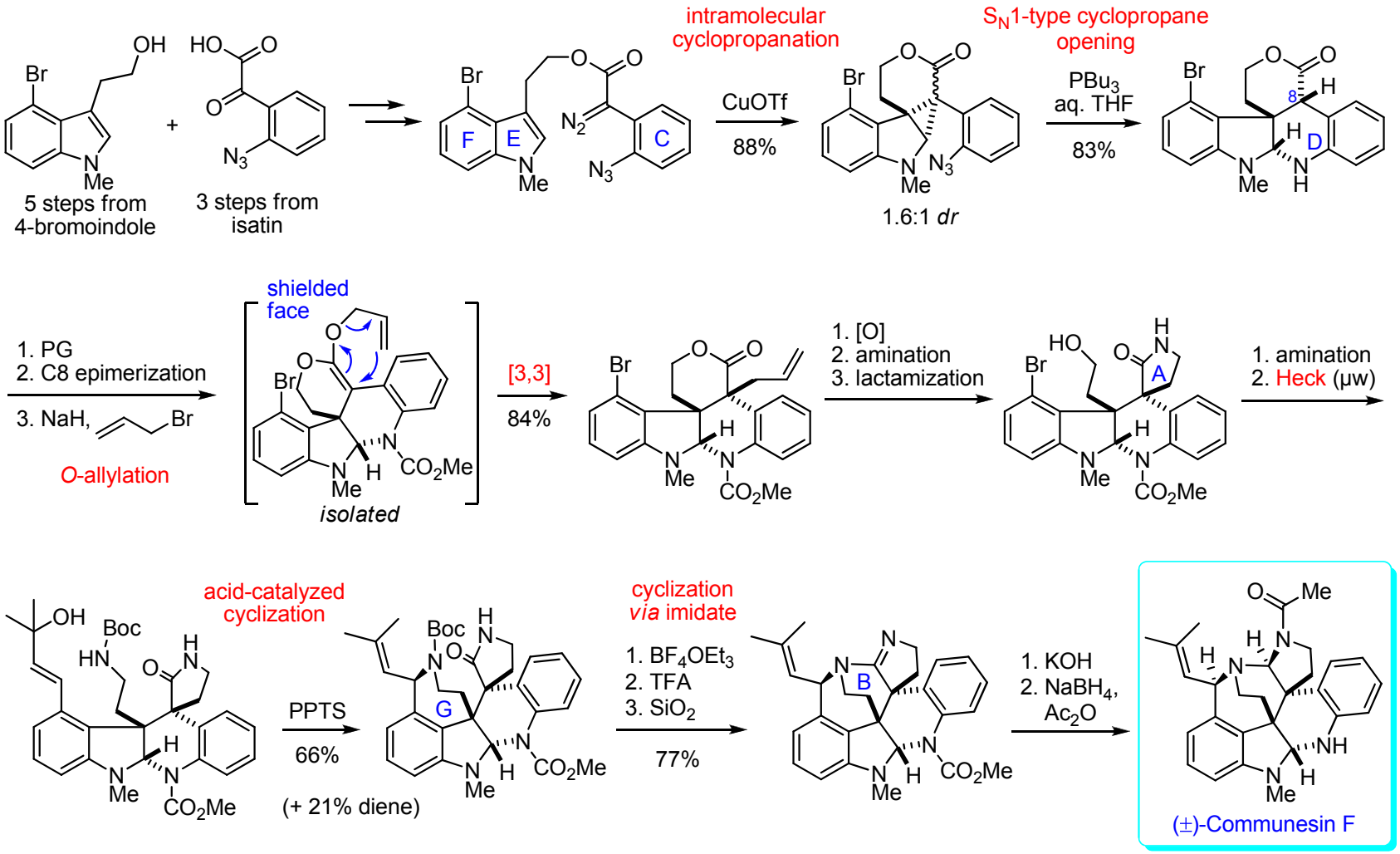


- Funk and Crawley (2006): Fluoride-promoted ring opening of aziridine followed by intramolecular hetero-Diels-Alder cycloaddition



May, J. A.; Stoltz, B. M. *Tetrahedron* **2006**, *62*, 5262.
Crawley, S. L.; Funk, R. L. *Org. Lett.* **2006**, *8*, 3995.
For other studies: Crawley, S. L.; Funk, R. L. *Org. Lett.* **2003**, *5*, 3169. George, J. H.; Adlington, R. M. *Synlett* **2008**, 2093.
For total synthesis of related alkaloids: Artman III, G. D.; Weinreb, S. M. *Org. Lett.* **2003**, *5*, 1523. Fuchs, J. R.; Funk, R. L. *J. Am. Chem. Soc.* **2004**, *126*, 5068. Sabahi, A.; Novikov, A.; Rainier, J. D. *Angew. Chem. Int. Ed.* **2006**, *45*, 4317. Shen, L.; Zhang, M.; Wu, Y.; Qin, Y. *Angew. Chem. Int. Ed.* **2008**, *47*, 3618.
For a short review: Siengalewicz, P.; Gaich, T.; Mulzer, J. *Angew. Chem. Int. Ed.* **2008**, *47*, 8170.

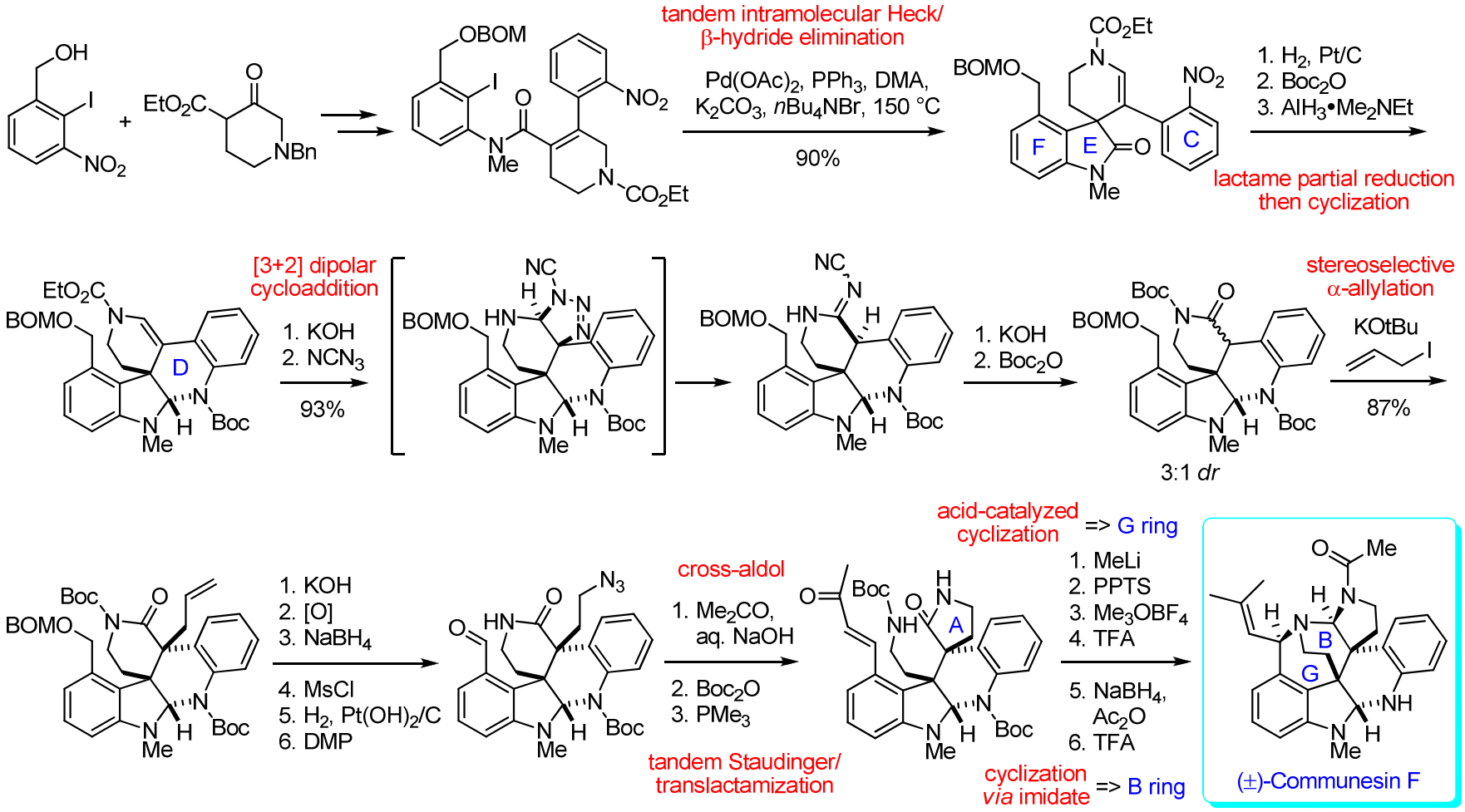
(±)-Communesin F: Qin's synthesis (2007)



- 30 steps (longest linear sequence) from commercially available material
- 1.2% overall yield

Yang, J.; Wu, H.; Shen, L.; Qin, Y. *J. Am. Chem. Soc.* **2007**, *129*, 13794.

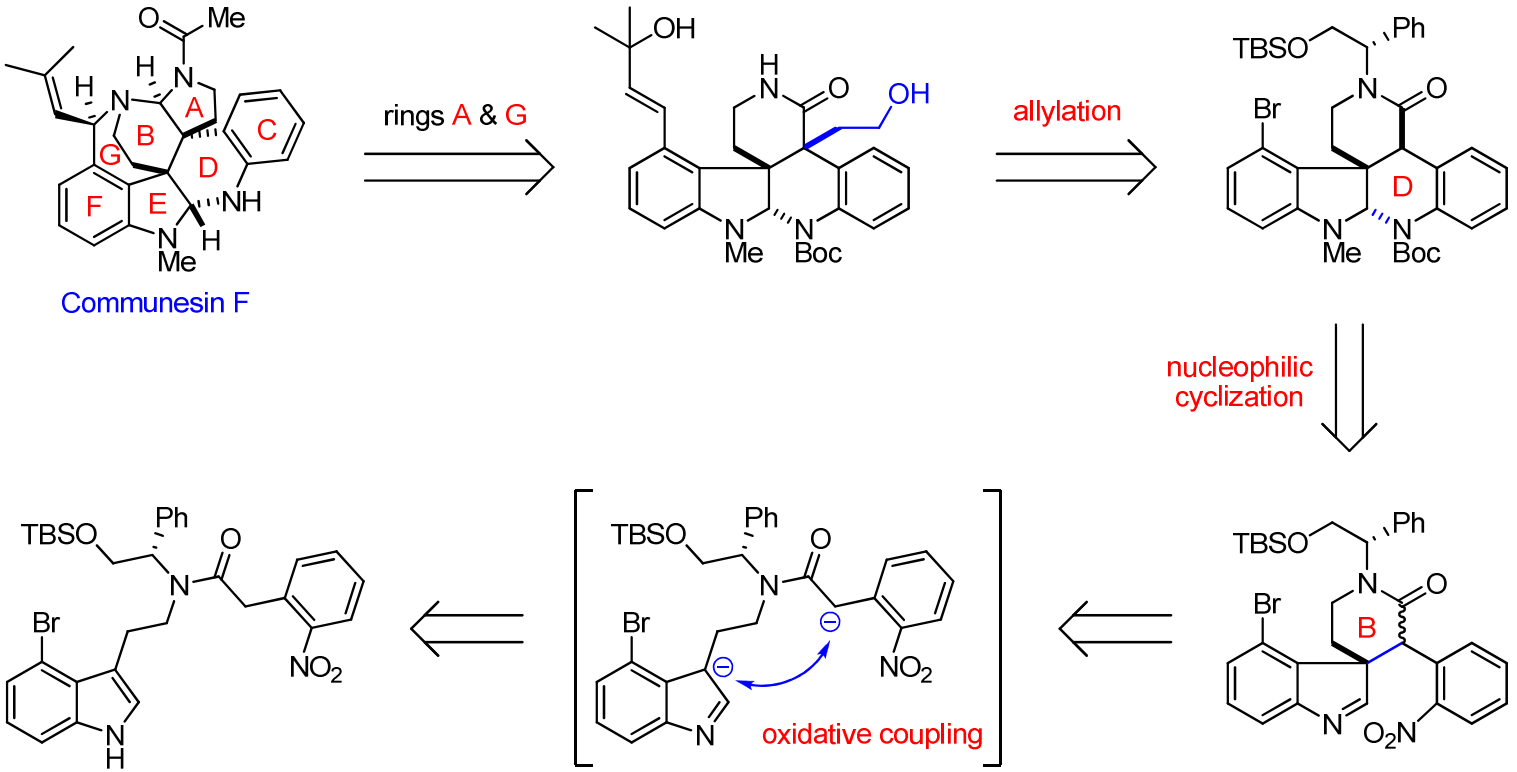
(±)-Communesin F: Weinreb's synthesis (2010)



- 31 steps (longest linear sequence) from commercially available material
- 0.9% overall yield

Liu, P.; Seo, J. H.; Weinreb, S. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 2000.

Title Paper: Communesin F Retrosynthetic Analysis



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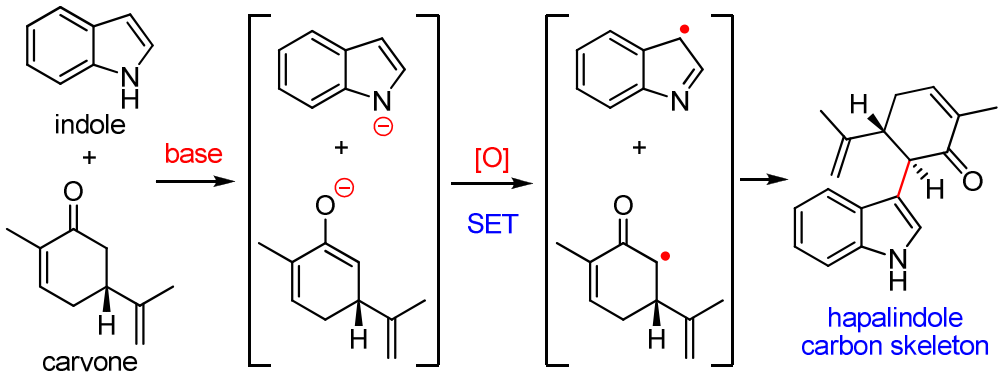
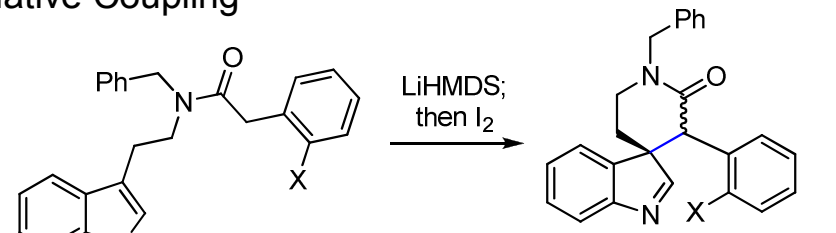
Oxidative coupling of indoles and pyrroles

Baran's Mechanistic Rationale in Developing the Oxidative Indole (and Pyrrole) Coupling Reaction

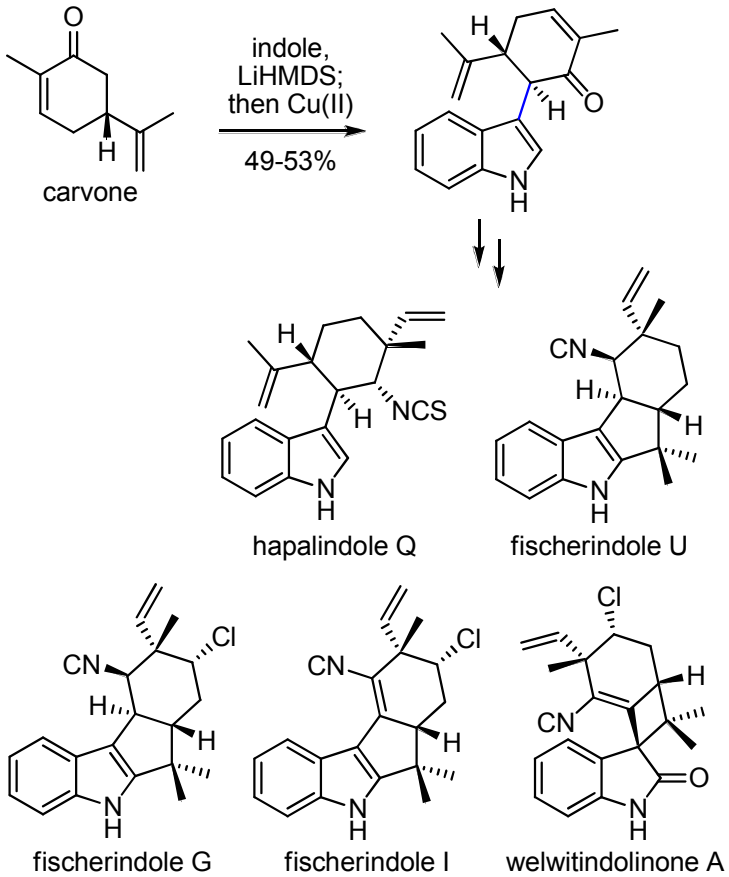


Application by Ma: Model Reaction for Intramolecular Oxidative Coupling



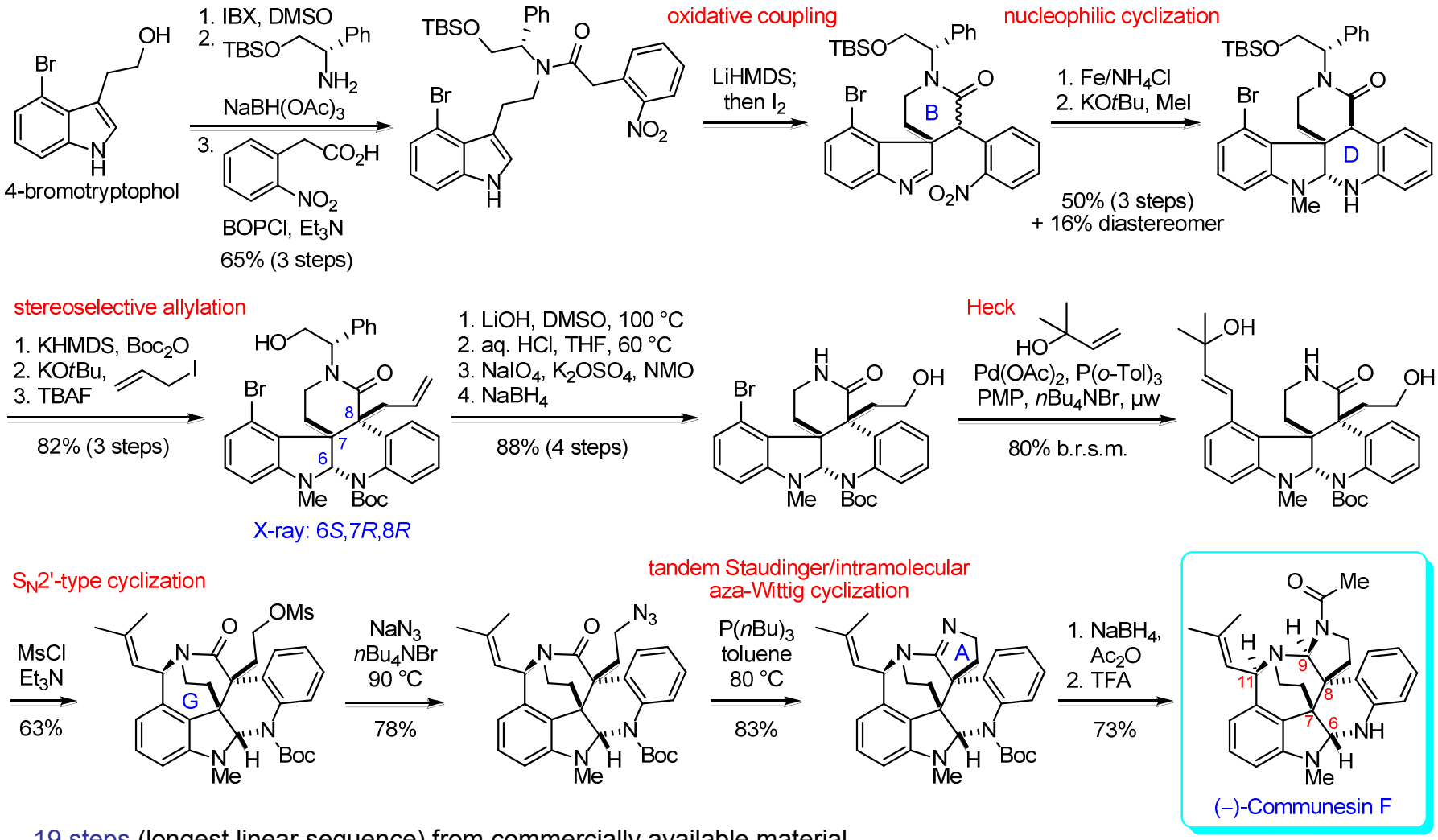
Zuo, Z.; Xie, W.; Ma, D. *J. Am. Chem. Soc.* **2010**, *132*, 13226.

Application to the Total Synthesis of Hapalindole-type Alkaloids



Baran, P. S.; Richter, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 7450. Baran, P. S.; Richter, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 15394. Baran, P. S. *Angew. Chem. Int. Ed.* **2005**, *44*, 609. Baran, P. S.; DeMartino, M. P. *Angew. Chem. Int. Ed.* **2006**, *45*, 7083. Richter, J. M.; Whitefield, B. W.; Maimone, T. J.; Lin, D. W.; Castroviejo, M. P.; Baran, P. S. *J. Am. Chem. Soc.* **2007**, *129*, 12875. Richter, J. M.; Idhihara, Y.; Masuda, T.; Whitefield, B. W.; Llamas, T.; Pohjakallio, A.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 17938.

(–)-Communesin F Total Synthesis: Title Paper



- 19 steps (longest linear sequence) from commercially available material
- 5.6% overall yield
- Absolute configuration of natural Communesin F assigned: 6*R*,7*R*,8*R*,9*S*,11*R*.

Zuo, Z.; Xie, W.; Ma, D. *J. Am. Chem. Soc.* **2010**, *132*, 13226.

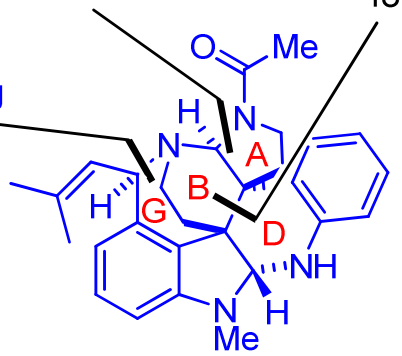
Conclusion and Perspectives

- Concise asymmetric total synthesis of (–)-Communesin F.
- Absolute stereochemical assignment of natural Communesin F.
- Key steps:

Final-stage introduction of A ring *via* tandem Staudinger/intramolecular aza-Wittig reaction with twisted amide

Mesilate-mediated formation of G ring

Unprecedented intramolecular oxidative coupling strategy and use of TBS-protected (S)-phenylglycinol as a chiral auxiliary for asymmetric formation of the spiro-fused indoline moiety (B ring)



- Comparison of synthetic routes (from commercially available materials):

	Qin	Weinreb	Ma
Longest linear sequence (steps)	30	31	19
Overall yield (%)	1.2	0.9	5.6

- Perspectives: further applications of the spiro-fused indoline formation *via* an intramolecular oxidative coupling to the synthesis of related indole alkaloids.