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Catalytic Asymmetric Total Synthesis of (−)-Actinophyllic Acid

L. Cai, K. Zhang, O. Kwon *J. Am. Chem. Soc.* **2016**, *138*, 3298.

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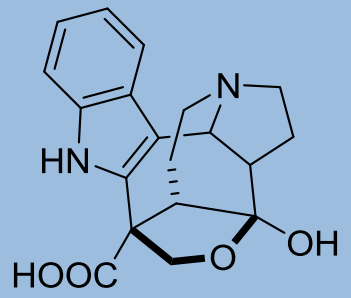

(-)-Actinophyllic acid

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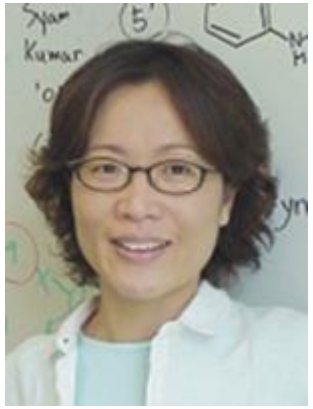
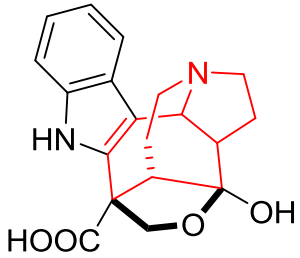
- B.S. and M.S. from Seoul National University, South Korea
- PhD. at Prof. S. J. Danishefsky (Columbia University)
- Postdoc in S. L. Schreiber's lab (Harvard University)
- Since 2001 UCLA as an assistant professor



- Research:
  - development of new nucleophilic phosphine catalysis reactions, new reaction methodologies
  - total synthesis of natural products
  - diversity-oriented combinatorial synthesis

(−)-Actinophyllic Acid

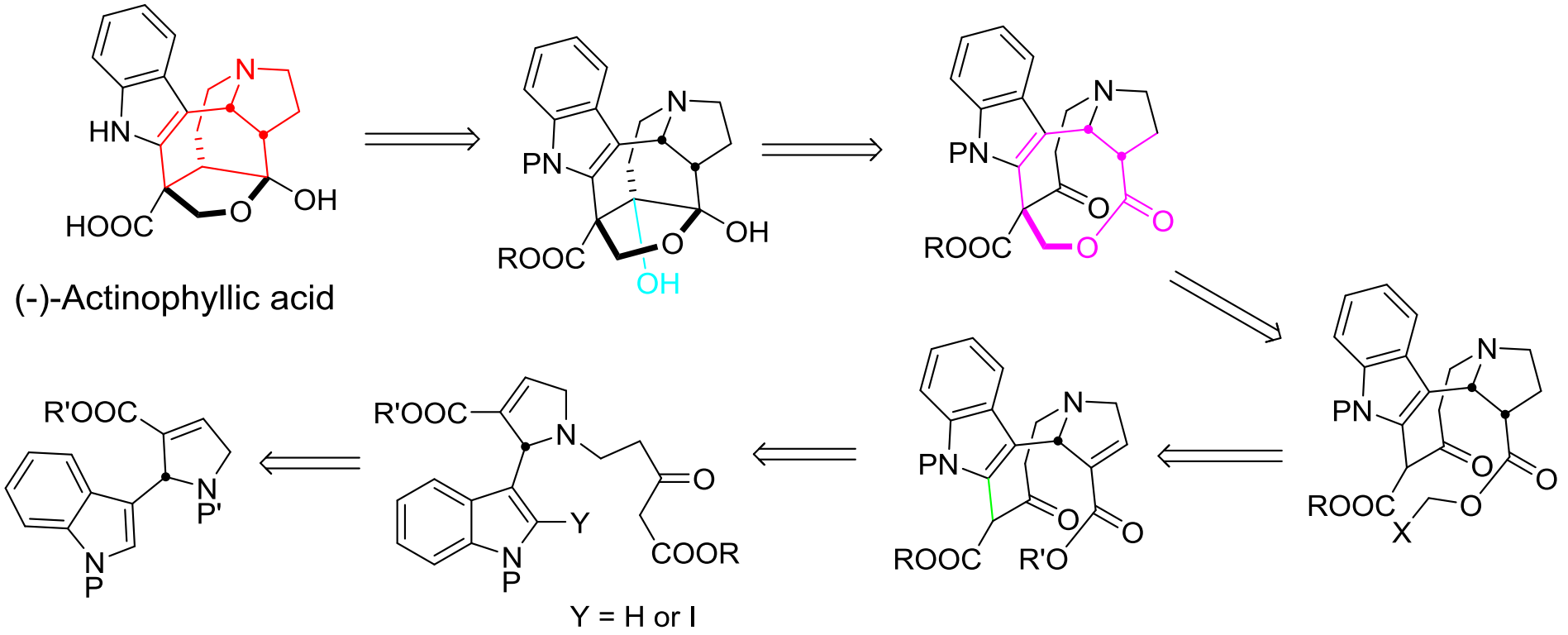


- first isolated in 2005 from the leaves of the tree *Alstonia actinophylla* in Australia
- therapeutic agent for the treatment of cardiovascular disorders

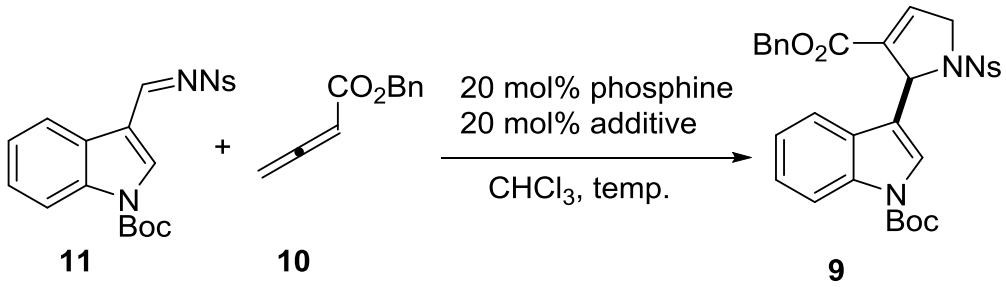
- low isolation yield (0.0072%)
- cage-like scaffold of 1,2,3,5,6,7,8,10a-octahydro-1,7-methanopyrrolo-[1,2-a]azocine
- 5 stereogenic centers

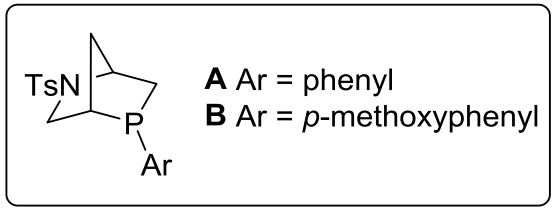
Martin, C. L.; Overman, L. E.; Rohde, J. M. *J. Am. Chem. Soc*. **2008**, *130*, 7568.
Martin, C. L.; Overman, L. E.; Rohde, J. M. *J. Am. Chem. Soc*. **2010**, *132*, 4894.
Granger, B. A.; Jewett, I. T.; Butler, J. D.; Hua, B.; Knezevic, C. E.; Parkinson, E. I.; Hergenrother, P. J.; Martin, S. F. *J. Am. Chem. Soc*. **2013**, *135*, 12984.
Galicia, I. Z.; Maldonado, L. A. *Tetrahedron Lett*. **2013**, *54*, 2180.

Retrosynthetic Analysis



Phosphine-Catalyzed Pyrrolidine Synthesis

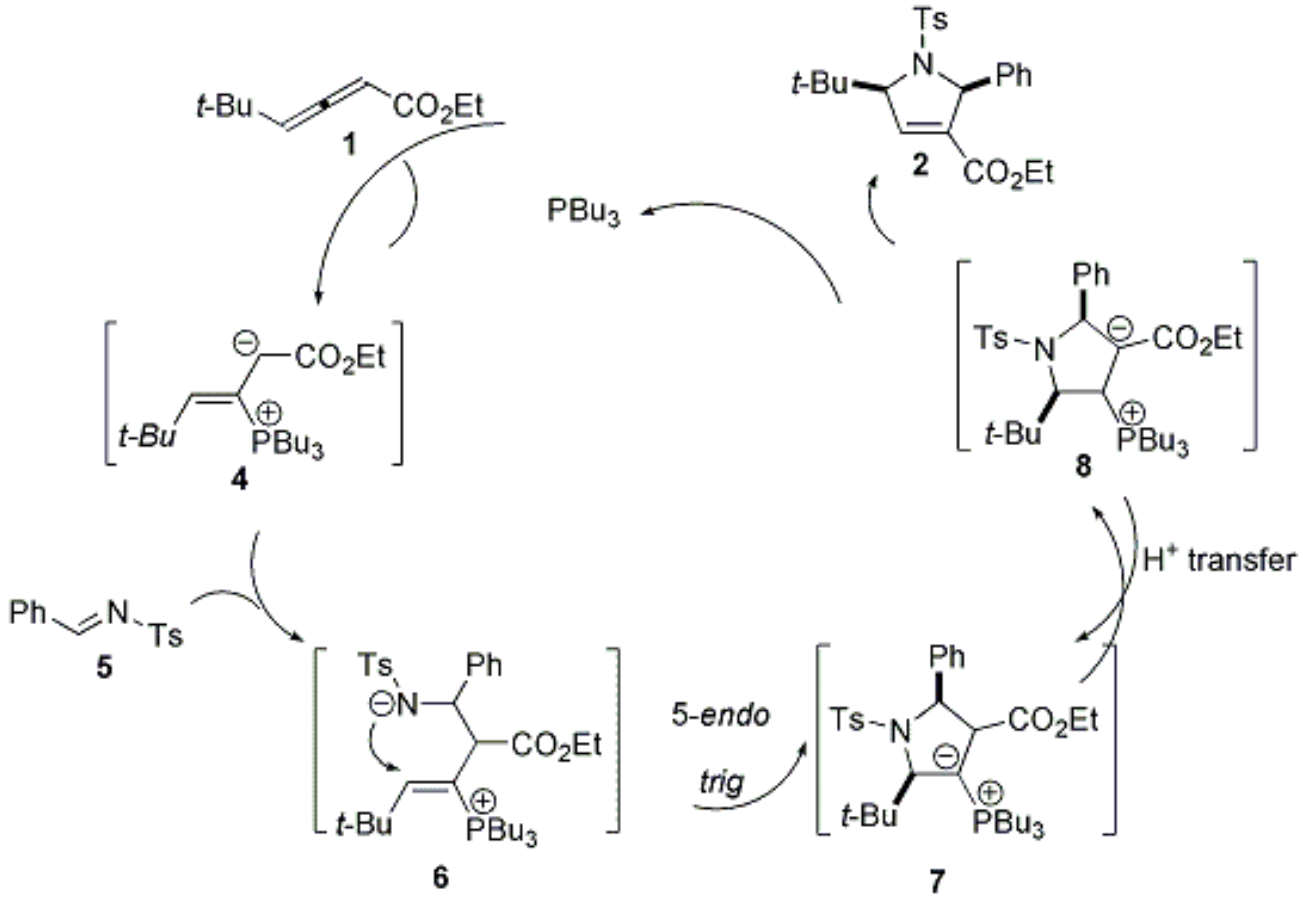


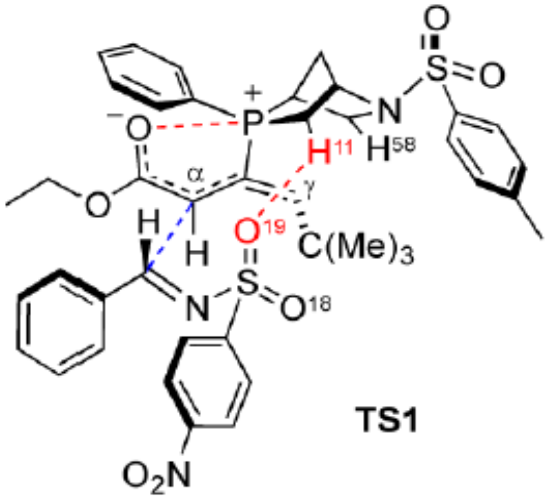


entry	cat.	temp. (°C)	additive	time (h)	yield (%)[a]	ee (%)[b]
1	PPh_3	rt		6	99	
2	A	rt		5	97	75
3	B	rt		5	99	83
4	B	0		5	99	91
5	B	0	phenol	2	99	91
6	B	0	biphenol	2	99	91
7	B	0	*s*-BINOL	2	99	94
8	B	0	*r*-BINOL	2	99	94

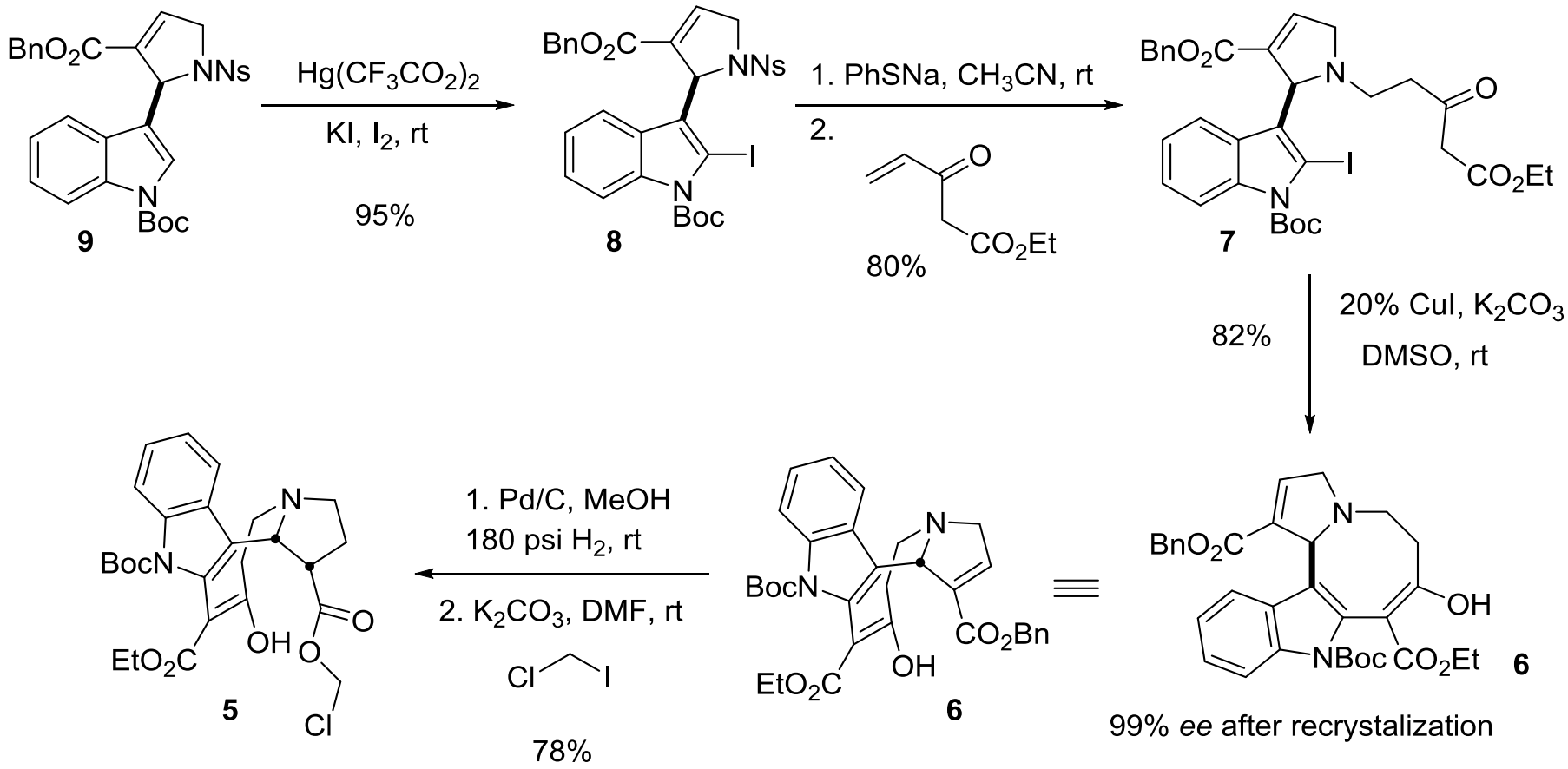
[a]Isolated yield after silica gel FCC. [b]Determined using HPLC.

Phosphine-catalyzed [3+2] Annulation of allenoates and imines

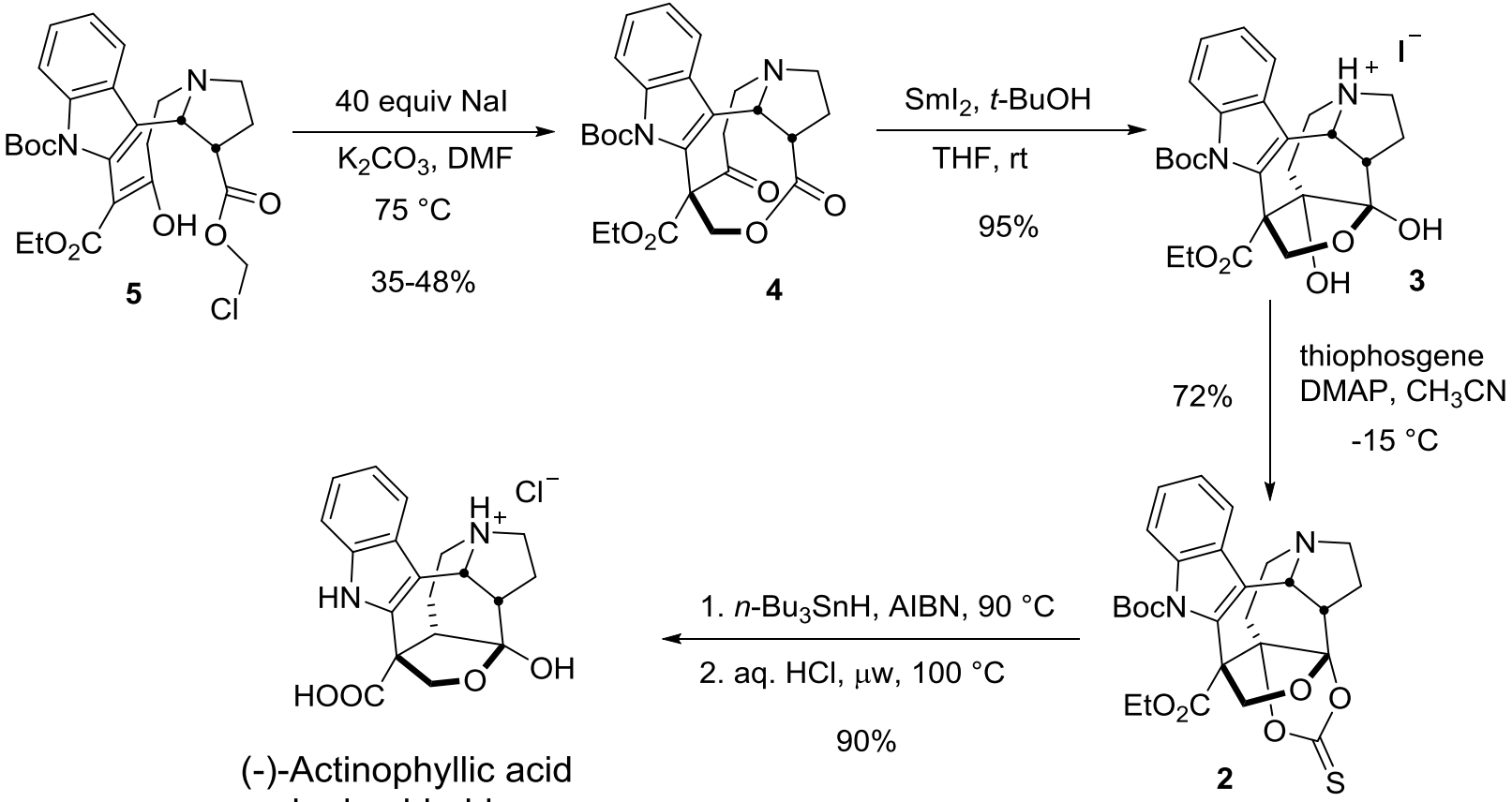


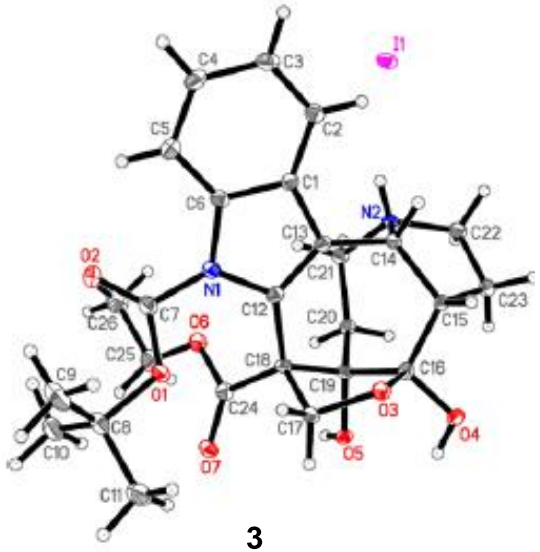


Forward Synthesis



Forward Synthesis





Conclusion

- asymmetric total synthesis of (−)-actinophyllic acid in 13 steps from a known aldehyde in 12.4% yield

- Key steps:
  - chiral phosphine-catalyzed [3+2] annulation between an allenoate and indole imine
  - CuI-catalyzed coupling between a 2-iodoindole and ketoester
  - intramolecular alkylative lactonization
  - pinacol coupling