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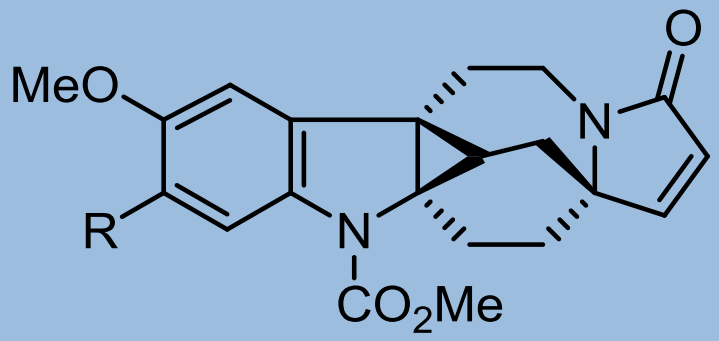
Total Synthesis of (-)-Lundurine A and Determination of Absolute Configuration



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Valentin Soulard

January 15, 2015

Yong Qin

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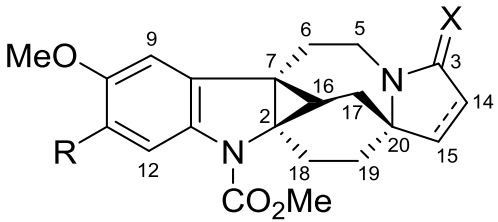
- 1992-1995 : PhD in the Institute of Chemistry, Chinese Academy of Sciences, with Prof. Zhitang Huang and Yaozhong Jiang
- 1995-1996 : Assistant Professor, Associate Professor of Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences
- 1996-2000 : Postdoc Associate, in the University of Vermont, with Prof. Martin E. Kuehne
- 2000-2003 : Research scientist, Triad Therapeutics Inc., San Diego
- Since 2003 : Prof. in West China School of Pharmacy, Sichuan University

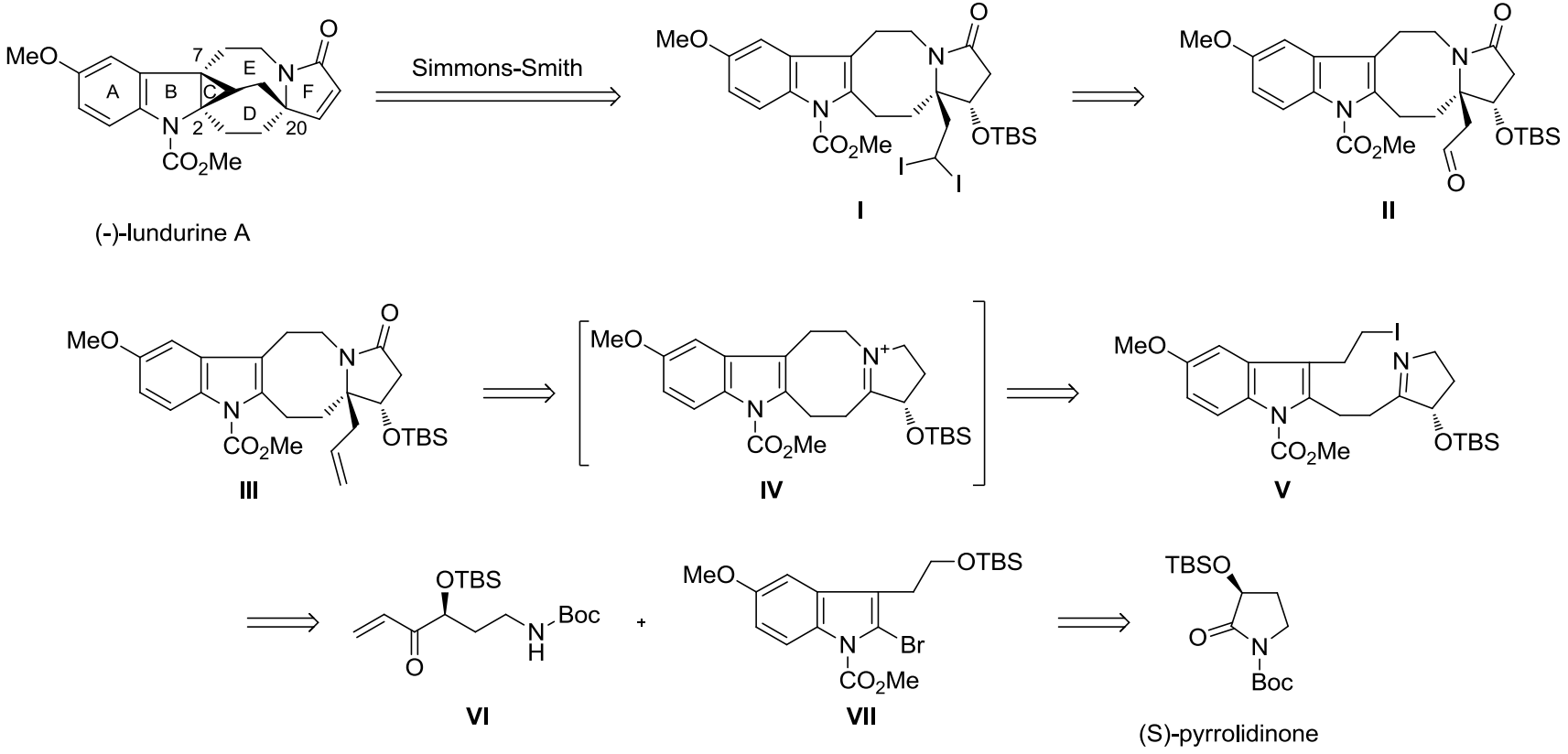
Lundurines A-D

- *Kopsia* alkaloid isolated from Malaysian *Kopsia tenuis*
- Effective at bypassing multidrug resistance in vincristine-resistant
- Lundurines B and D show promising in vitro cytotoxic activity against B16 melanoma cells
- Attractivies for their biological activities and their unusual polycyclic skeleton.
- Only racemic and long synthesis were reported before.

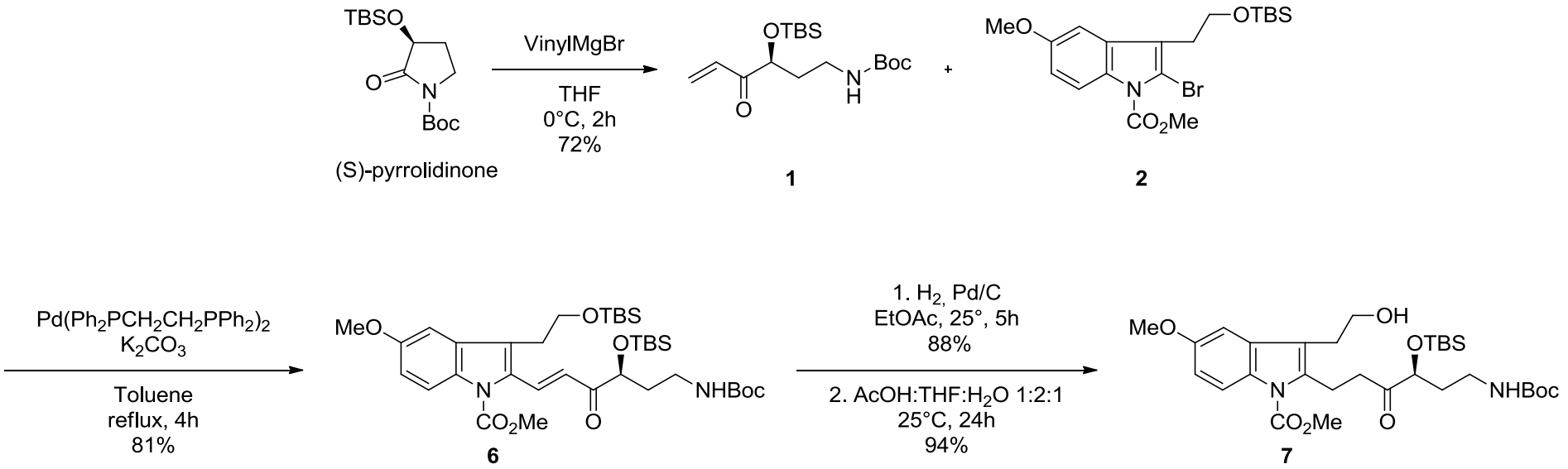


Lundurine A : R = H, X= O,$\Delta^{14, 15}$
Lundurine B : R = H, X= H_2, $\Delta^{14, 15}$
Lundurine C : R = H, X= H_2
Lundurine D: R = OMe, X= H_2, $\Delta^{14, 15}$

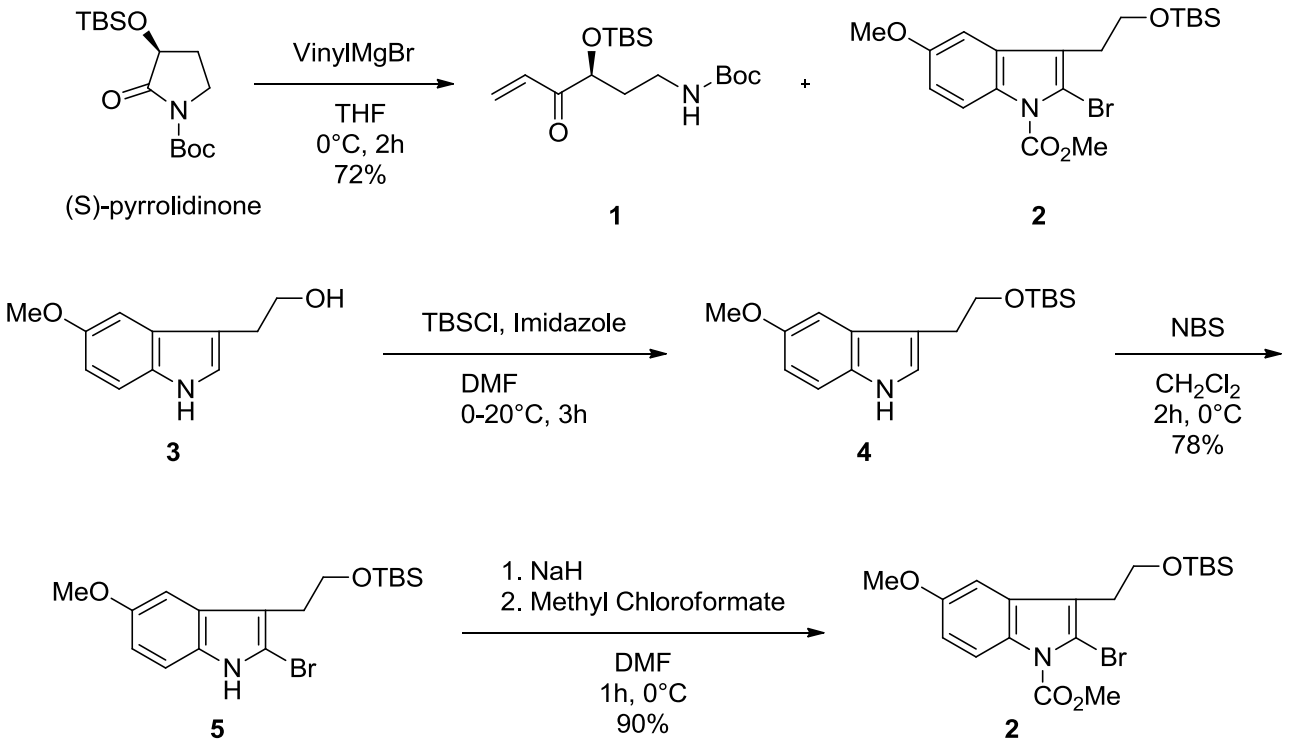
Retrosynthetic analysis of lundurine A



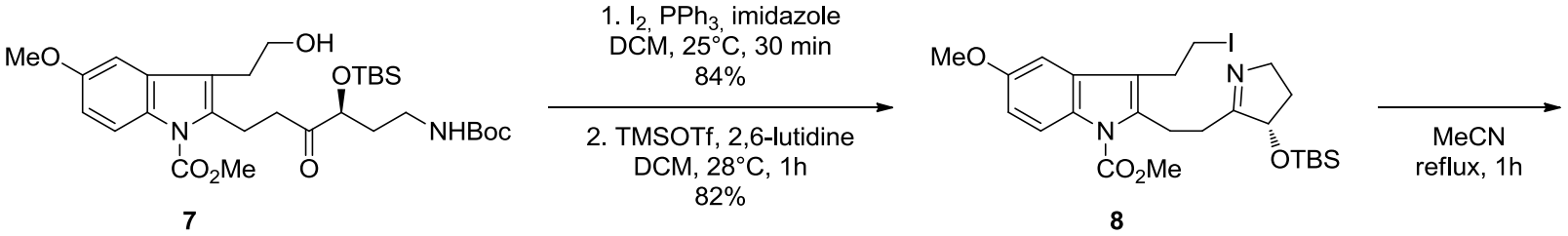
Total Synthesis of (-)-Lundurine A

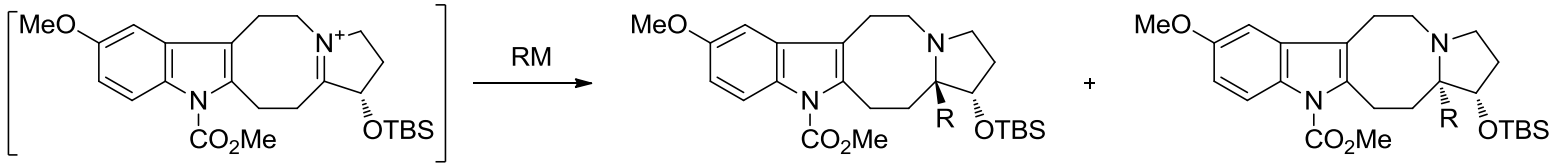


Total Synthesis of (-)-Lundurine A



Synthesis of (-)-Lundurine A





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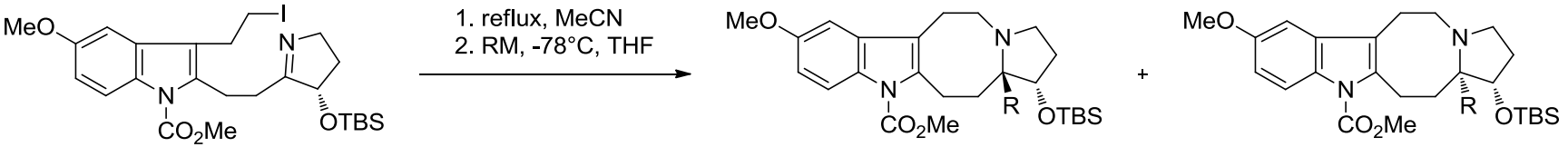


8

10 - Major

10' - Minor

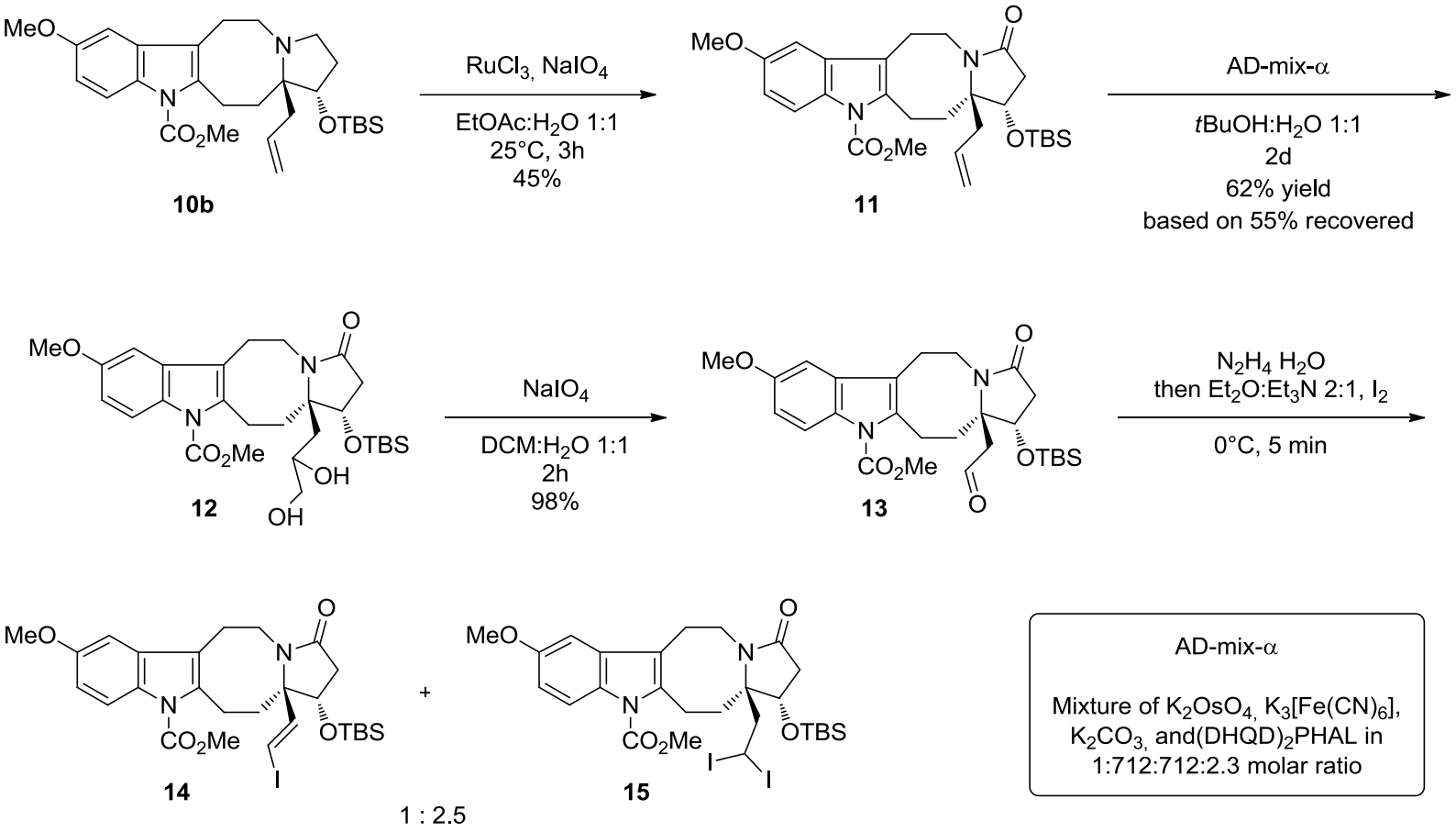
10a, R = CH_2CO_2Et
10b, R = vinyl
10c, R = allyl

10'a, R = CH_2CO_2Et
10'b, R = vinyl
10'c, R = allyl

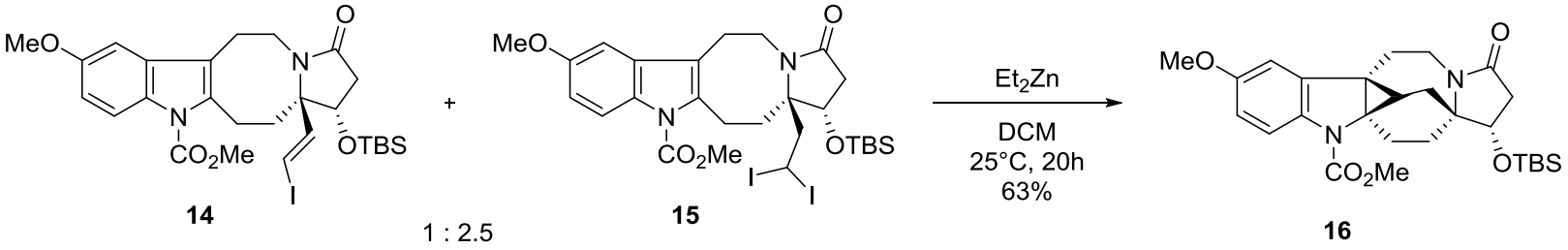
Entry	Reagent	Yield of **10**[a]	Ratio (**10**:**10'**)[b]
1	EtOAc/LDA	41 (**10a**+**10'a**)	1:1
2	EtOAc/LiHMDS	46 (**10a**+**10'a**)	2:1
3	EtOAc/NaHMDS	27 (**10a**+**10'a**)	6:1
4	VinylMgBr	62 (**10b**+**10'b**)	>30:1
5	AllylMgBr	65 (**10c**+**10'c**)	5:1

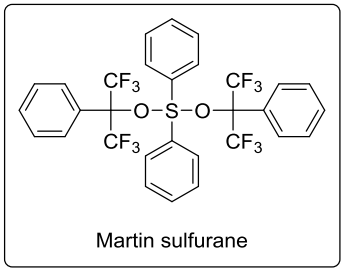
a. Yield of isolated product.
b. Ration was determined by ^{1}H NMR analysis of the crude product

Synthesis of (-)-Lundurine A



Synthesis of (-)-Lundurine A





Conclusion

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- First asymmetric and concise total synthesis of (-)-lundurine A in 15 steps (overall yield : 2 %)
- Stereoelective organometallic addition on a iminium generated in situ
- Formation of the cyclopropyl C ring, the six-membered D ring, and the seven membered E ring, together with the quaternary carbon stereocenters at C2 and C7 only with a Simmon-smith reaction,

Thank you for your attention !