A Concise Enantioselective Total Synthesis of (–)-Deoxoapodine

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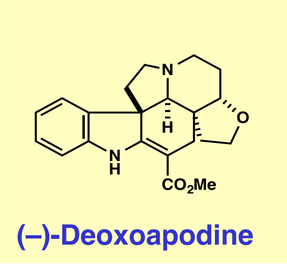
1. Introduction



(–)-Deoxoapodine

- Isolation and Structural Determination: Diatta, L. *et al. Rev. CENIC, Cienc. Fis.* 1975, *6*, 135. Poter, P. *et al. Pytochem.* 1980, *19*, 1473.
- Racemic Syntheses: Overman, L. E. *et al. J. Am. Chem. Soc.* 1991, *113*, 2598. Boger, D. L. *et al. J. Am. Chem. Soc.* 2014, *136*, 3312.
- Asymmetric Syntheses: Hoveyda, A. H.; Movassaghi, M. *et al. Angew. Chem. Int. Ed.* 2017, *56*, 13857. Peng, X. S. *et al. J. Org. Chem.* 2020, *85*, 967. Tokuyama, H. *et al. Angew. Chem. Int. Ed.* (DOI: 10.1002/anie. 202010759).

Vobtusine

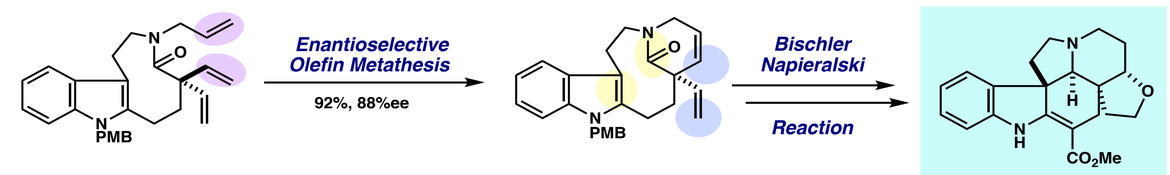
- Isolation and Structural Determination: Wenkert, E. *et al. J. Org. Chem.* 1976, *41*, 3270.
- Biological Activity: Cytotoxicity against HL60 cells

Voacandimine A

- Isolation and Structural Determination: Takayama, H. *et al. Tetrahedron* 2013, *69*, 796.
- Biological Activity: Cannabinoid Receptor (CB1) Antagonist (Illicit Drugs)

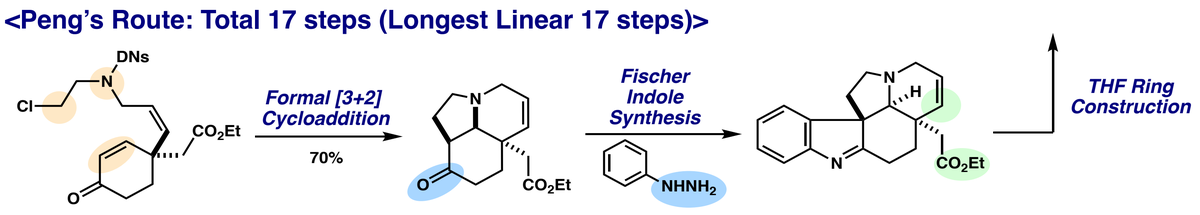
2. Asymmetric Total Syntheses of Deoxoapodine

<Movassaghi's Route: Total 22 steps (Longest Linear 17 steps)>



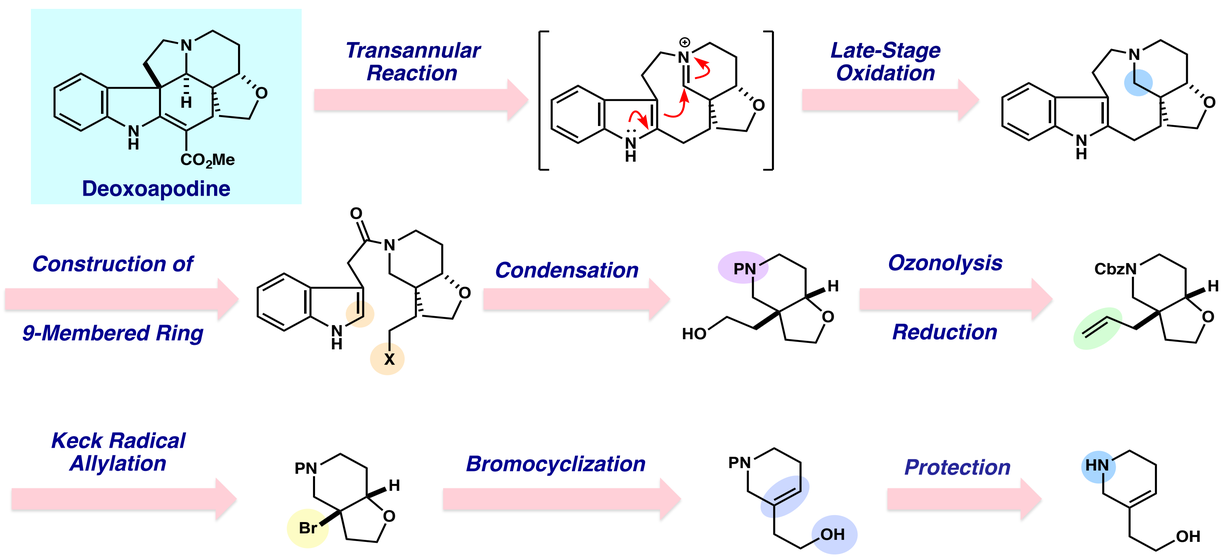
Hoveyda, A. H.; Movassaghi, M. *et al. Angew. Chem. Int. Ed.* 2017, *56*, 13857.

<Peng's Route: Total 17 steps (Longest Linear 17 steps)>



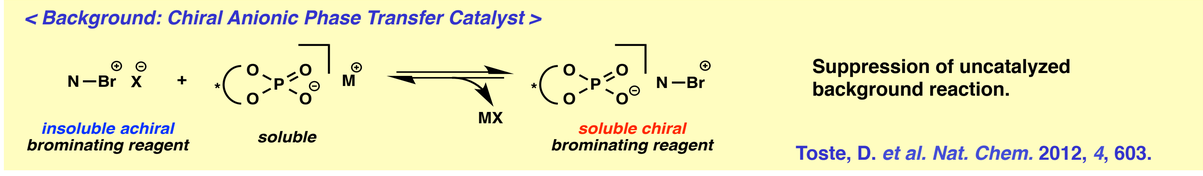
Peng, X. S. *et al. J. Org. Chem.* 2020, *85*, 967.

3. Retrosynthetic Analysis of Deoxoapodine

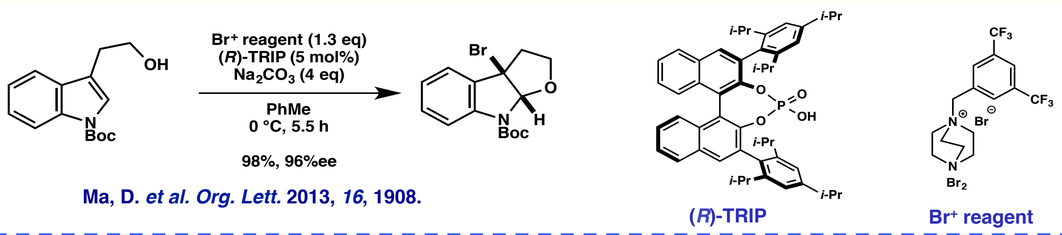


5. Optimization of Enantioselective 5-endo-trig Bromocyclization

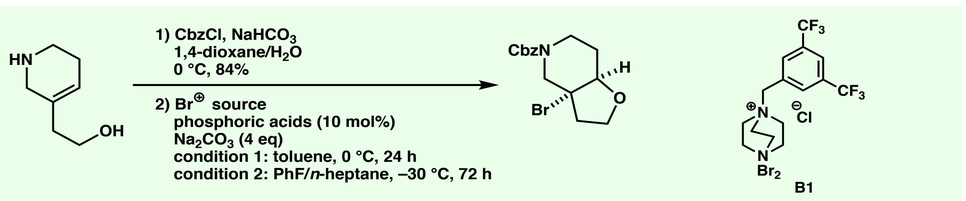
< Background: Chiral Anionic Phase Transfer Catalyst >

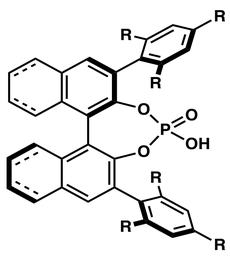


Toste, D. *et al. Nat. Chem.* 2012, *4*, 603.

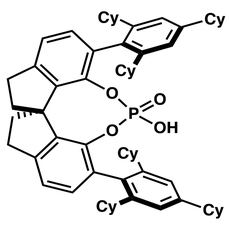


Ma, D. *et al. Org. Lett.* 2013, *16*, 1908.

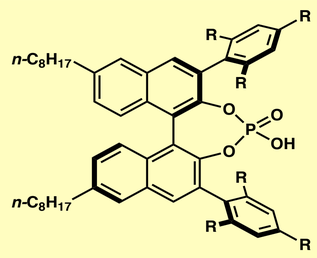




R = *i*-Pr (*R*)-TRIP: 77%, 52%ee (condition 1)
R = *i*-Pr (*R*)-H_8-TRIP: 71%, 45%ee (condition 1)
R = Cy (*R*)-TCYP: 59%, 64%ee (condition 1)
R = Cy (*R*)-H_8-TCYP: 72%, 65%ee (condition 1)

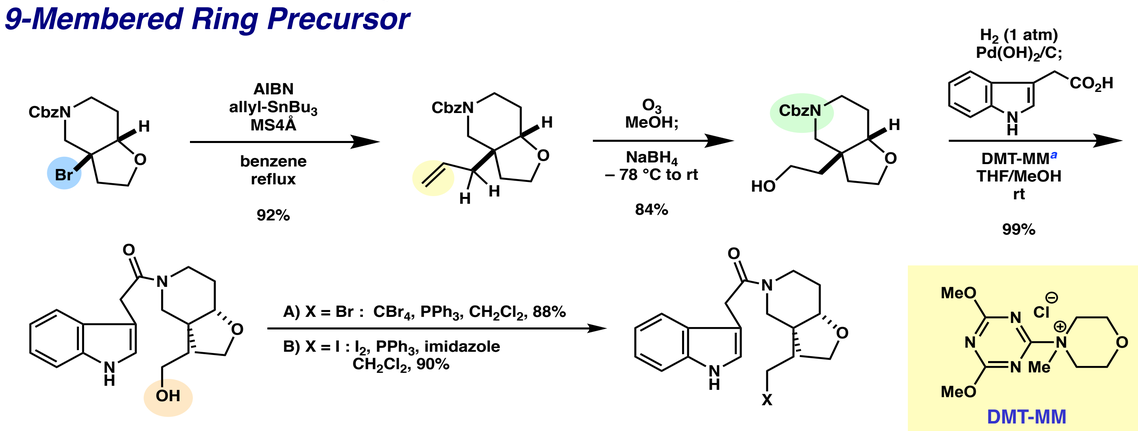


(*R*)-STCYP, 46%, –70%ee (condition 1)



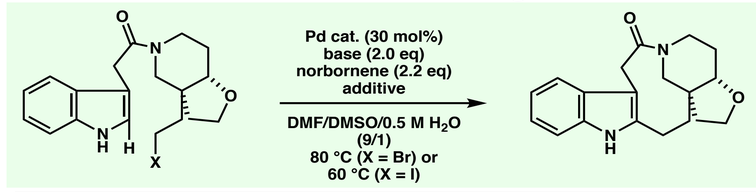
R = *i*-Pr (*R*)-C_8-TRIP: 75%, 50%ee (condition 1)
R = Cy (*R*)-C_8-TCYP: 75%, 70%ee (condition 1)
R = Cy (*R*)-C_8-TCYP: 80%, 84%ee (condition 2)
R = Cy (*S*)-C_8-TCYP: 76%, –86%ee (condition 2)

6. Construction of Quaternary Carbon Center and Preparation of 9-Membered Ring Precursor



[a] Kunishima, M. *et al. Tetrahedron* 2001, *57*, 1551.

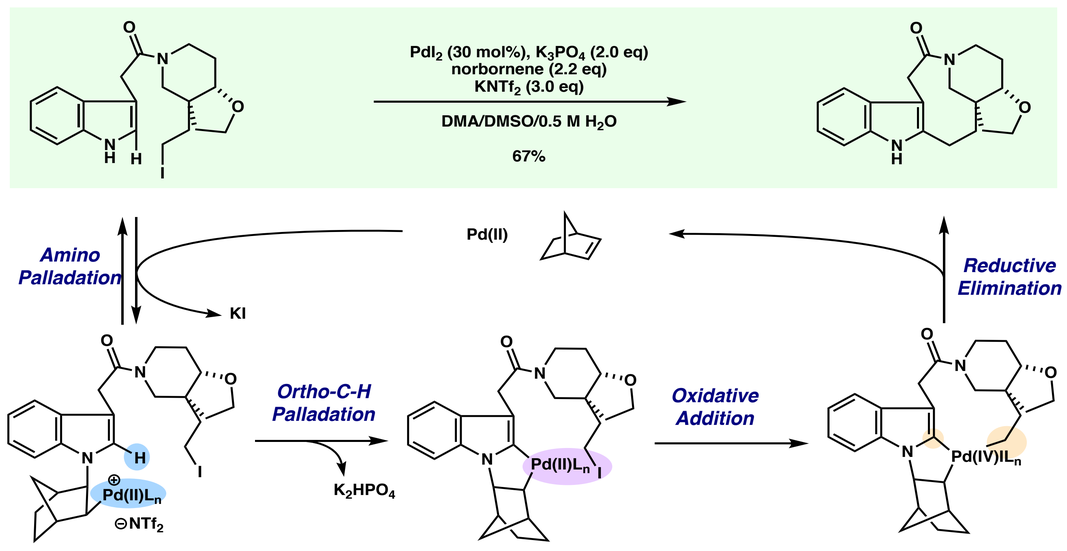
7. Optimization of Construction of 9-membered Ring



entry	X	Pd cat.	base	additive	time (h)	yield (%)
1	Br	$PdCl_2$	K_2CO_3	–	120	9
2	Br	$PdBr_2$	K_2CO_3	–	7.5	28
3	Br	$PdBr_2$	K_3PO_4	–	7	27
4[a]	I	$PdBr_2$	K_3PO_4	–	30	31
5[a]	I	PdI_2	K_3PO_4	–	17	38
6[a]	I	PdI_2	K_3PO_4	NaOTf[b]	48	48
7[a]	I	PdI_2	K_3PO_4	$NaNTf_2$	48	55
8[a]	I	PdI_2	K_3PO_4	$KNTf_2$	10	67

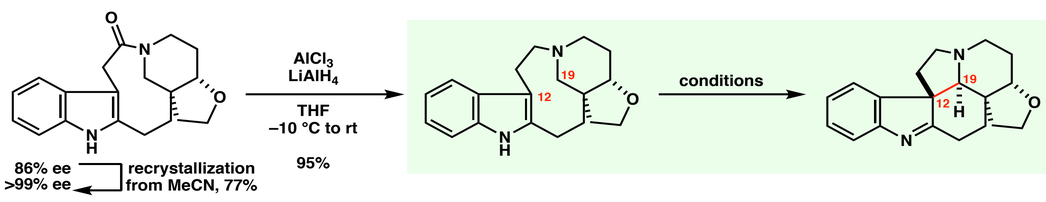
[a] DMA was used instead of DMF.
[b] Morken, J. P. *et. al. J. Am. Chem. Soc.* 2017, *139*, 3153.

7. Construction of 9-Membered Ring via C-H Alkylation

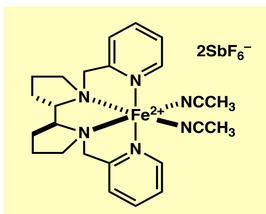


Bach, T. *et al. J. Am. Chem. Soc.* 2012, *134*, 14563.

8. Late-Stage Oxidative Transannular Reaction



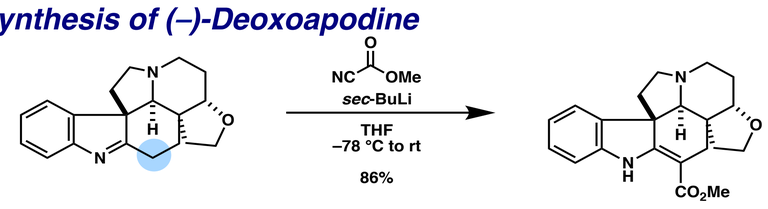
entry	reagents (eq.)	solvent	temp. (°C)	time (h)	yield (%)
1[a]	$Hg(OAc)_2$ (2.2)	AcOH	rt to reflux	24	decomp.
2[b]	PtO_2 (2.7), O_2 (1 atm)	EtOH	rt	24	decomp.
3[c]	$K_3Fe(CN)_6$ (10)	*t*-BuOH/H_2O	0	2	6
4[d]	I_2 (3), $NaHCO_3$	MeCN	0	0.5	6 (11 brsm)
5[e]	$Ru(bpy)_3Cl_2$ (0.1), bromomalonate	DMF	50	24	decomp.
6[f]	AcOH (10), O_2 (1 atm)	DCE	60	2	13
7[g]	Fe(*R*,*R*-PDP) (0.15), AcOH, 30% H_2O_2	*t*-BuOH	rt	3	22
8[g]	Fe(*S*,*S*-PDP) (0.03), AcOH, 30% H_2O_2	*t*-AmOH	rt	6	35 (42 brsm)



Fe(*S*,*S*-PDP)

[a] Kutney, J. P. *et al. J. Am. Chem. Soc.* 1970, *92*, 1700. [b] Schmid, H. *et al. Heiv. Chim. Acta.* 1963, *46*, 1996.
[c] Corey, E. J. *et al. J. Am. Chem. Soc.* 1999, *121*, 6771. [d] Gaichi, T. *et al. Chem. Commun.* 2017, *53*, 7451.
[e] Stephenson, C. R. J. *et al. Acc. Chem. Res.* 2015, *48*, 1474. [f] Tokuyama, H. *et al. Org. Lett.* 2014, *16*, 4149.
[g] White, M. C. *et al. Science* 2007, *318*, 783.

9. Total Synthesis of (–)-Deoxoapodine

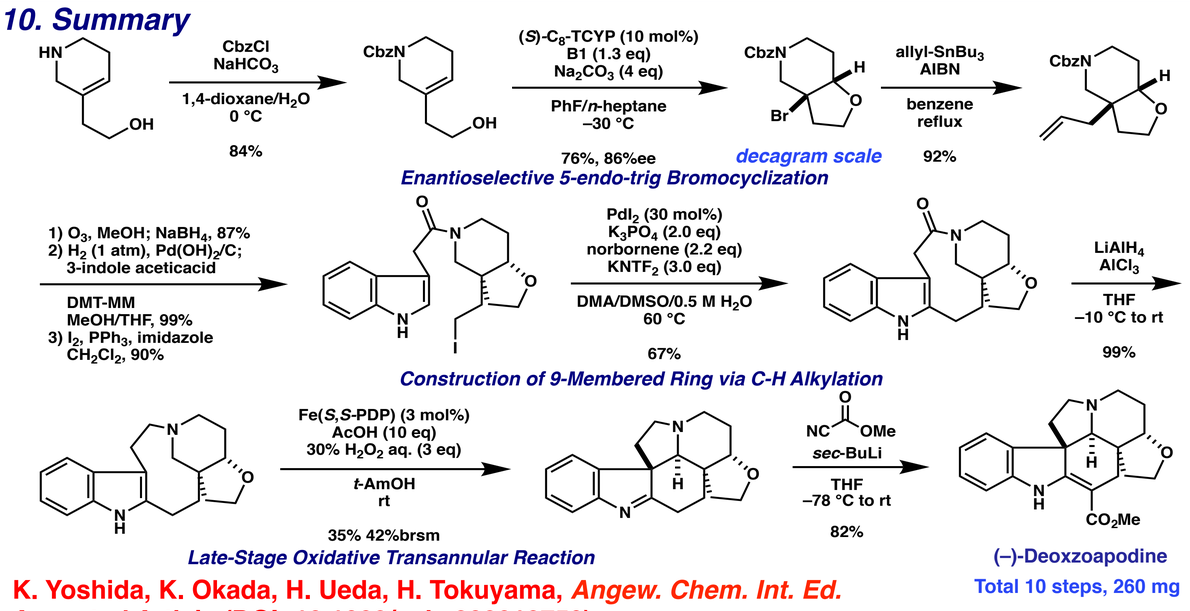


Total 10 steps
260 mg

[1] Movassaghi, M. *et al. Angew. Chem. Int. Ed.* 2017, *56*, 13857.

(–)-Deoxoapodine $[\alpha]_D^{25}$ = –497 (Lit.[1] $[\alpha]_D^{25}$ = –512)

10. Summary



K. Yoshida, K. Okada, H. Ueda, H. Tokuyama, *Angew. Chem. Int. Ed.* Accepted Article (DOI: 10.1002/anie.202010759).