

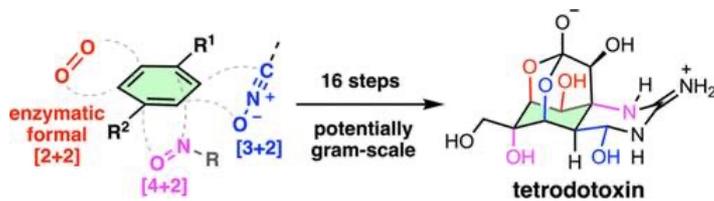
# 16-Step Scalable Chemoenzymatic Synthesis of Tetrodotoxin

Chen Peng,\* Weilin Wu,\* Yuxuan Ye,\* and Pengfei Hu\*

J. Am. Chem. Soc. 2026, 148, 4873-4879

neteroatom-to-carbonratio (1:1)

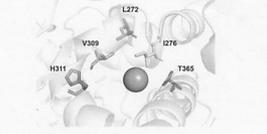
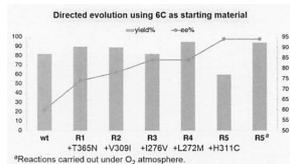
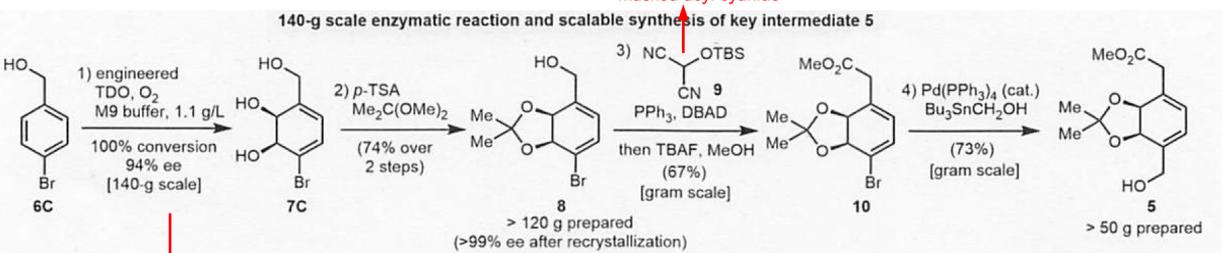
octa-substituted cyclohexane core



sequential triple difunctionalization

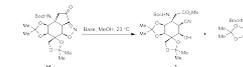
masked acyl cyanide

82% 62%ee → 94% 94%ee



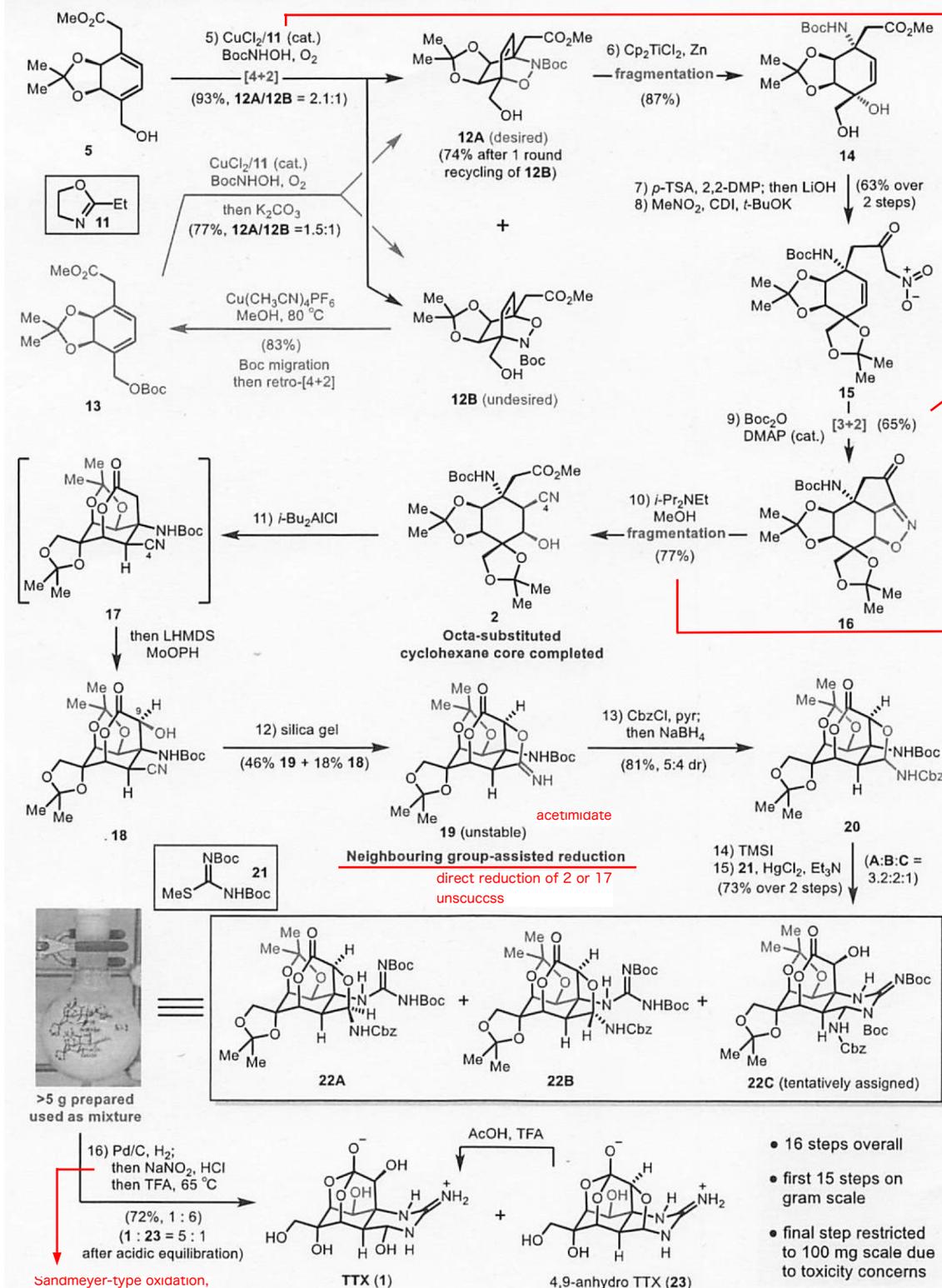
Entry	Reaction time (min)	Yield (%)	Enantiomeric ratio (%)
1	10	82	62
2	15	85	75
3	20	88	85
4	25	90	90
5	30	92	92
6	35	94	94

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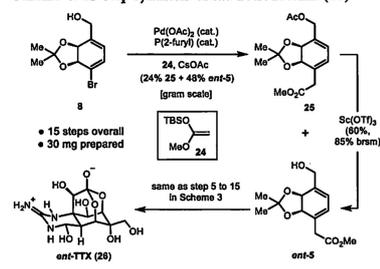


Entry	Conditions	Yield (%)	Enantiomeric ratio (%)
1	10	82	62
2	15	85	75
3	20	88	85
4	25	90	90
5	30	92	92
6	35	94	94

## Concise and Scalable Synthesis of Tetrodotoxin (1)



### Scheme 4. 15-Step synthesis of *ent*-Tetrodotoxin (26)



10 steps: strategic bond constructions with 2 fragmentation transformations  
4 steps onprotecting group and redox manipulations