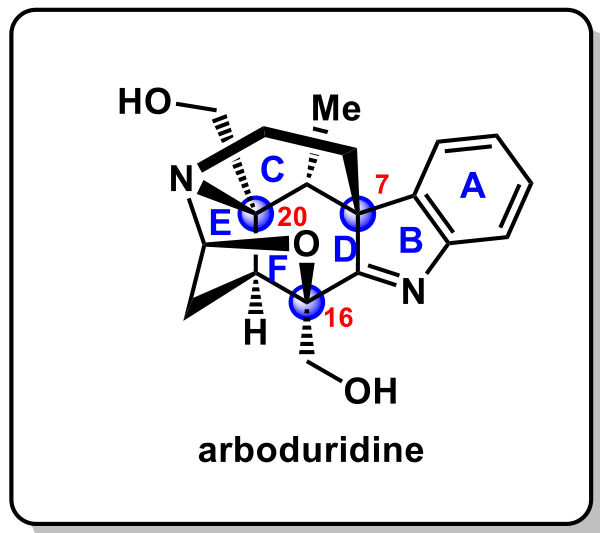


Total Synthesis

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doi.org/10.1002/anie.202316016

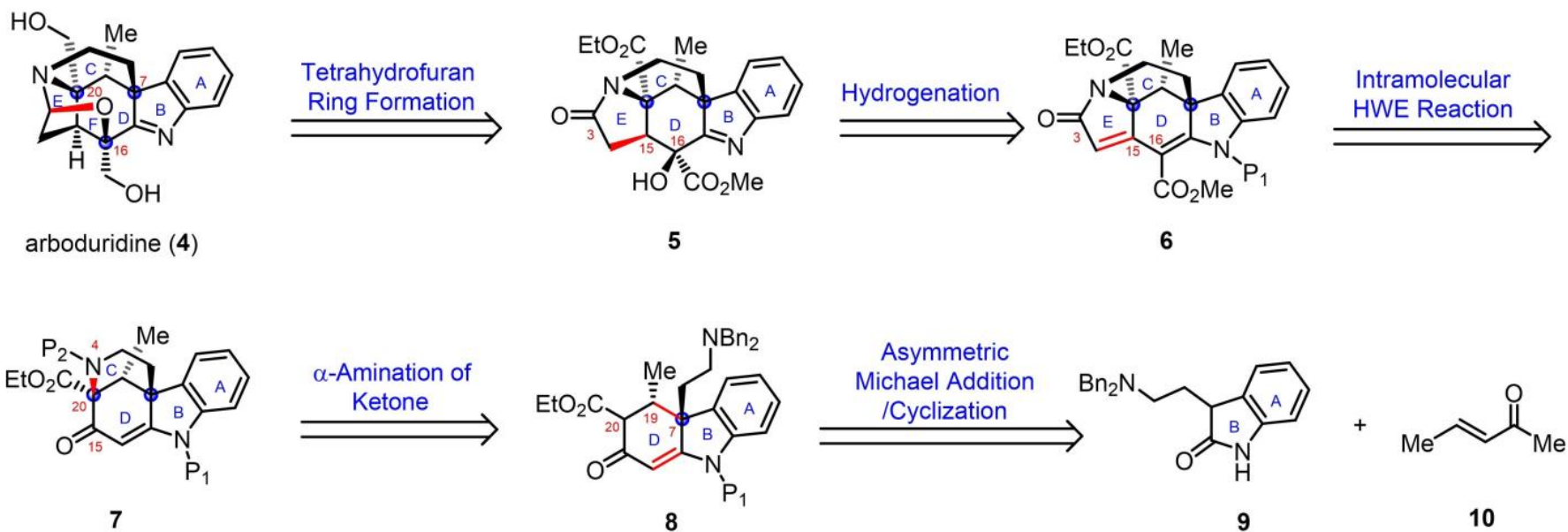
Asymmetric Synthesis of Arboduridine

Rui Yang⁺, Zeyu Zhou⁺, Huanfeng Jiang, Toh-Seok Kam, Kai Chen, and Zhiqiang Ma*

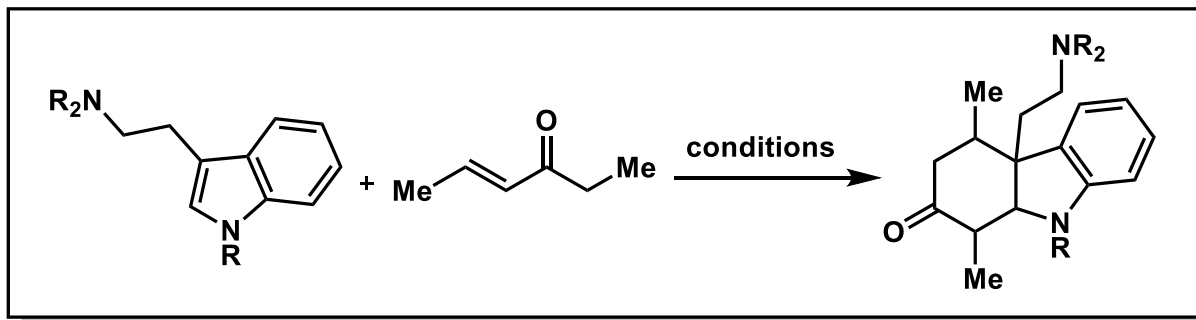


- ❑ Isolated by Kam from the Malayan *K. arborea* Blume in 2022
- ❑ Caged hexacyclic structure
- ❑ Five contiguous stereocenters

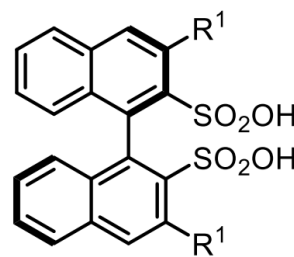
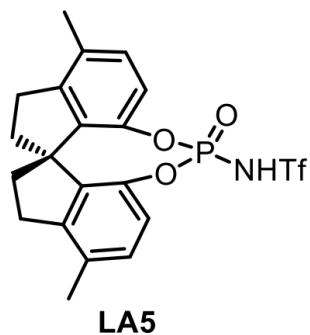
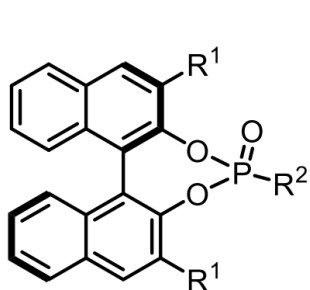
Retrosynthetic Analysis of Arboduridine



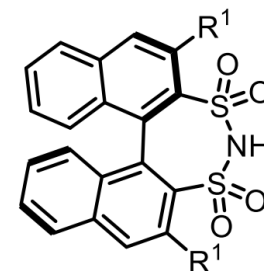
Attempts of Asymmetric Michael and Mannich Addition with Tryptamine Derivatives and S2



Brønsted acids



LA6: $R^1 = 3,5-(CF_3)_2C_6H_3$



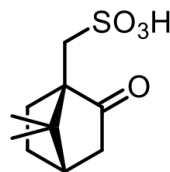
LA8: $R^1 = 3,5-(CF_3)_2C_6H_3$

LA1: $R^1 = Ph$, $R^2 = OH$;

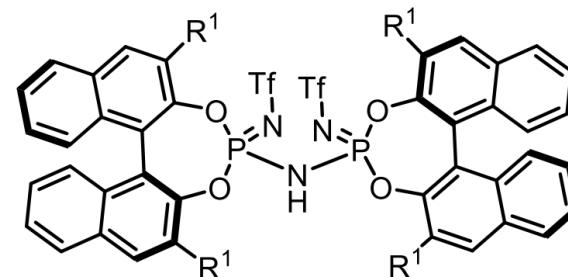
LA2: $R^1 = 2,4,6-(iPr)_3C_6H_2$, $R^2 = OH$;

LA3: $R^1 = SiPh_3$, $R^2 = NHTf$;

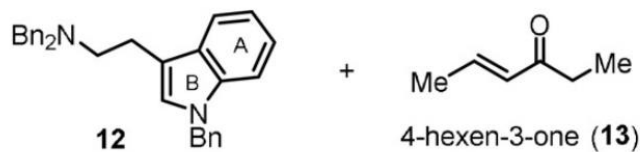
LA4: $R^1 = 3,5-(CF_3)_2C_6H_3$, $R^2 = NHTf$



LA7



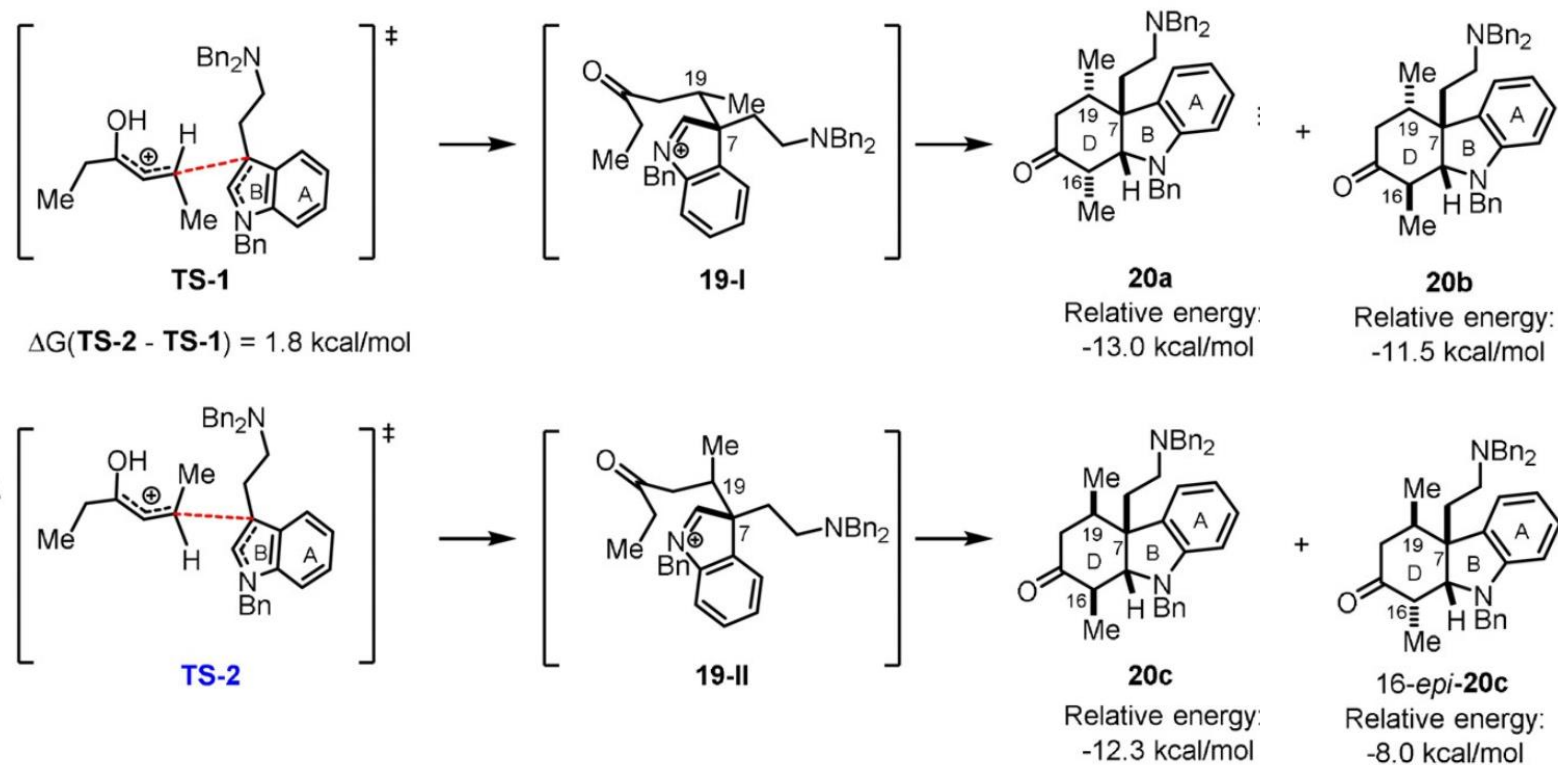
LA9: $R^1 = 3,5-(CF_3)_2C_6H_3$



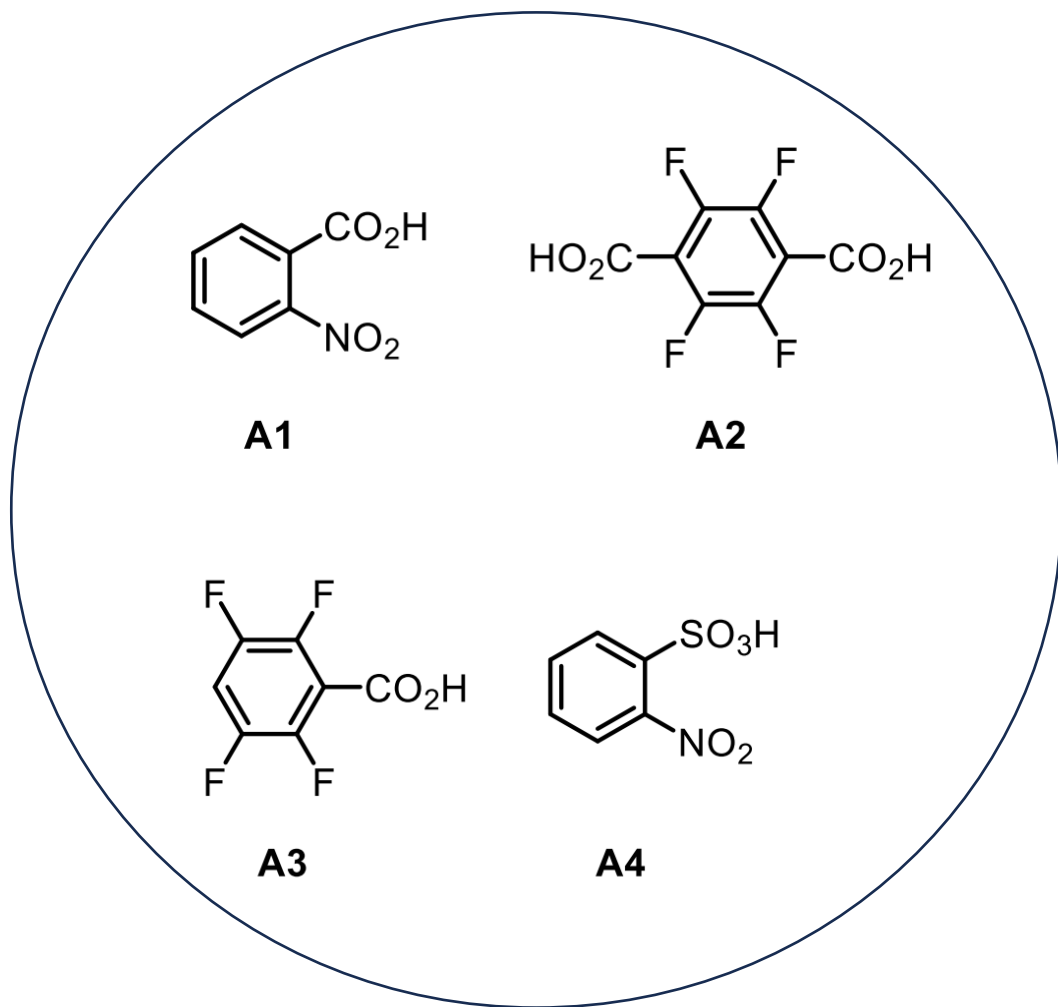
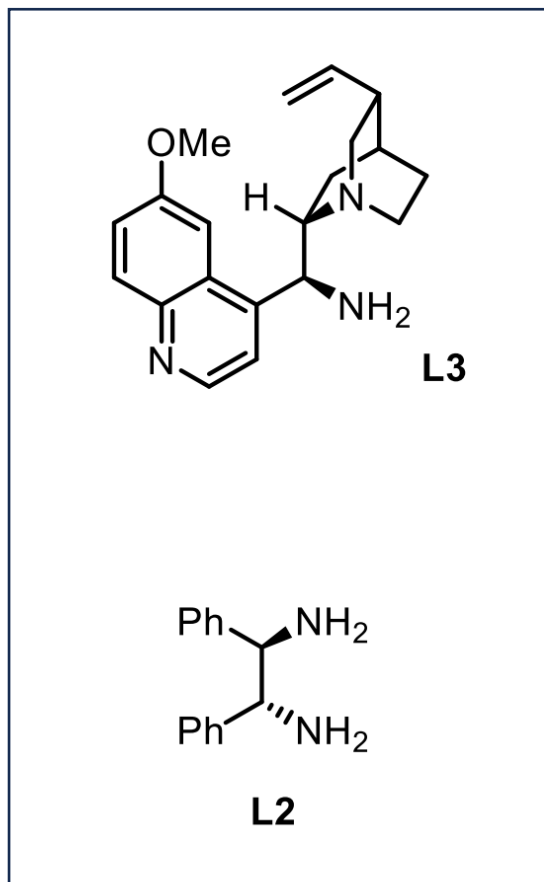
TfOH, MeCN, 0 °C to rt

20a: 44%; **20b**: 11%; **20c**: 30%; 16-*epi*-**20c**: 0%

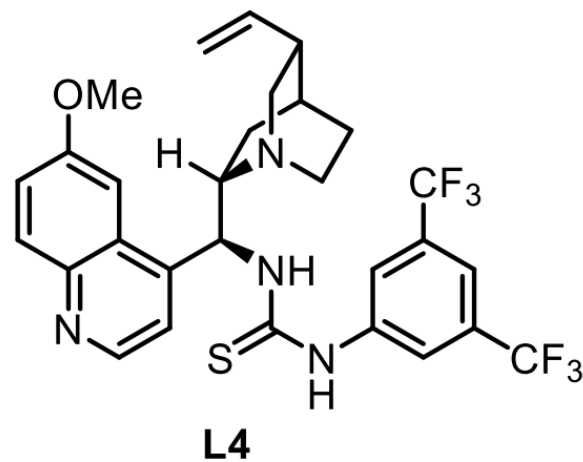
Cascade Michael/Mannich reactions



Primary amines catalysts with Brønsted acids



Thiourea type ligand



Macmillan's secondary amine catalyst

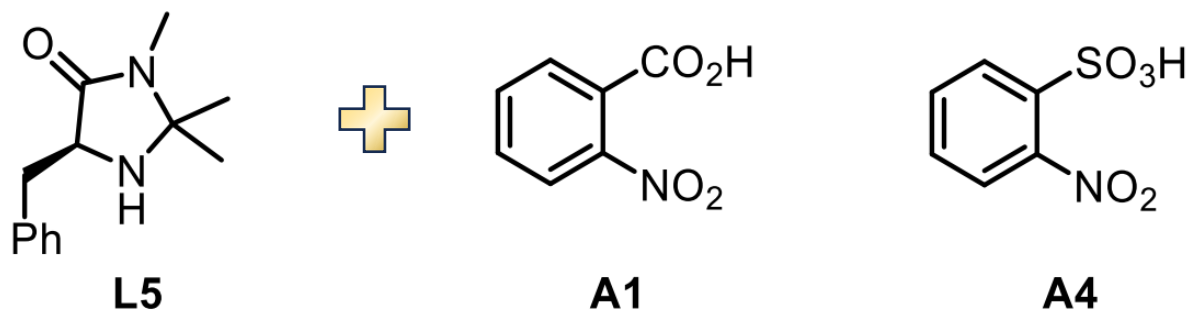
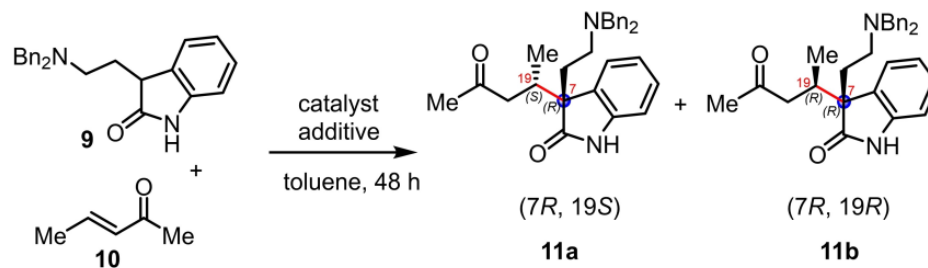
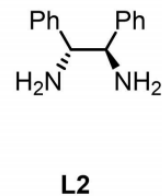
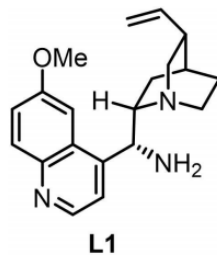


Table 1: Optimization of the *anti*-selective Michael addition of oxindole **9** to enone **10**.



Entry ^[a]	Cat. (mol%)	Additive	Yield of 11a + 11b [%] ^[b]	ee of 11a [%] ^[c]	dr of 11a/11b ^[d]
1	L1 (10)	<i>p</i> -TsOH	13	63	1.6:1
2	L2 (10)	<i>p</i> -TsOH	47	70	1.3:1
3	L2 (10)	<i>N</i> -Boc-D-Phg	78	88	2.8:1
4 ^[e,f]	L2 (20)	<i>N</i> -Boc-D-Phg	78	95	5.8:1
5 ^[e,f,g]	L2 (20)	<i>N</i> -Boc-D-Phg	95	96	5.5:1



Construction of A/B/D Ring System

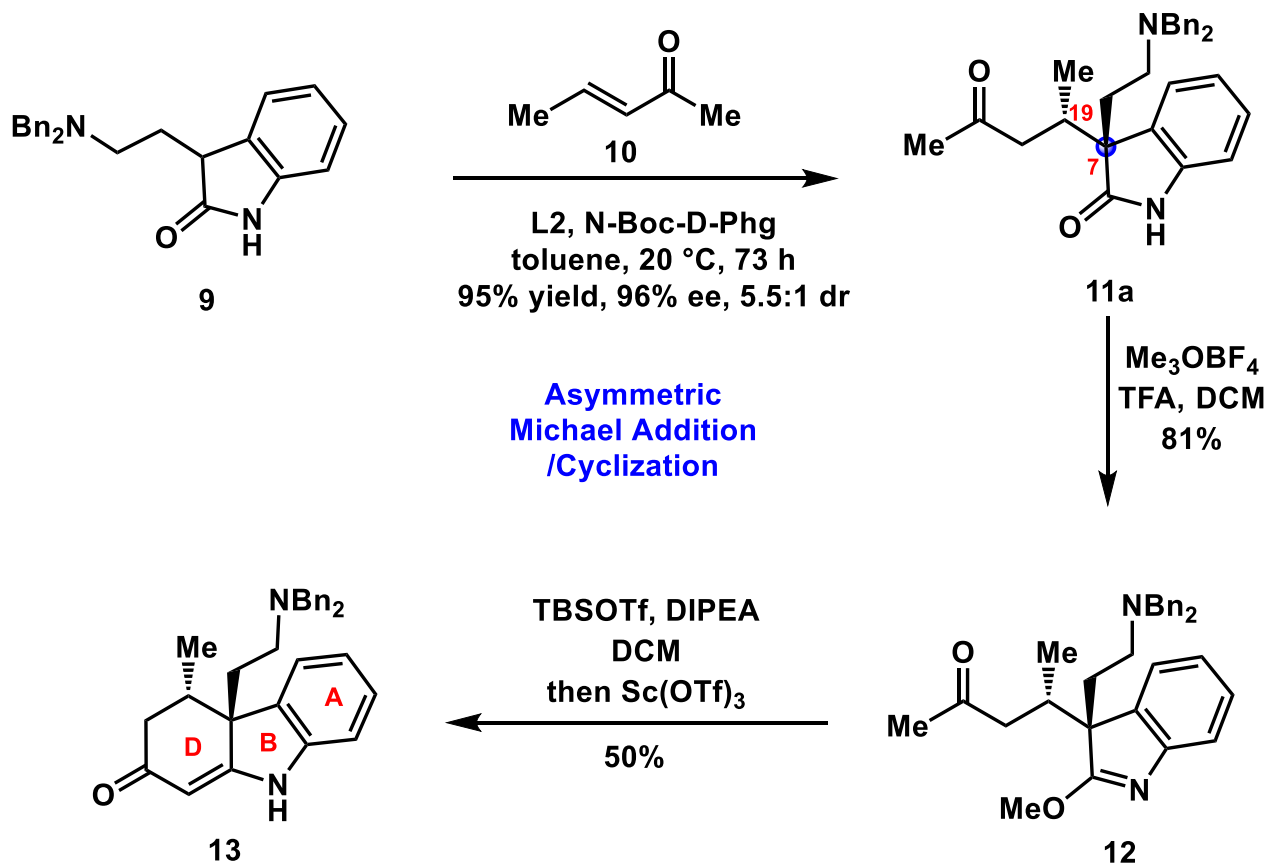
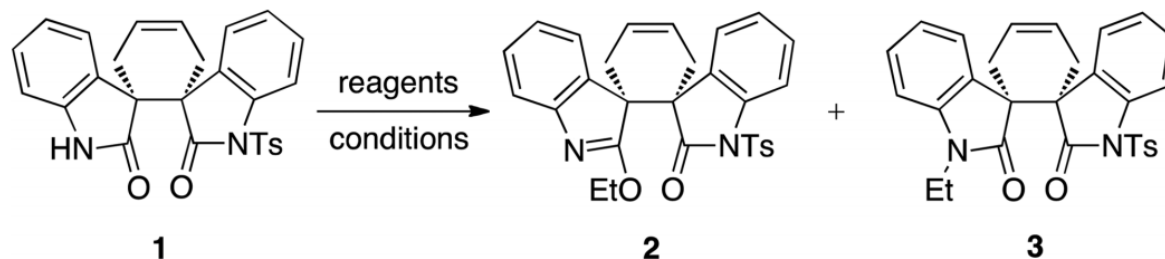


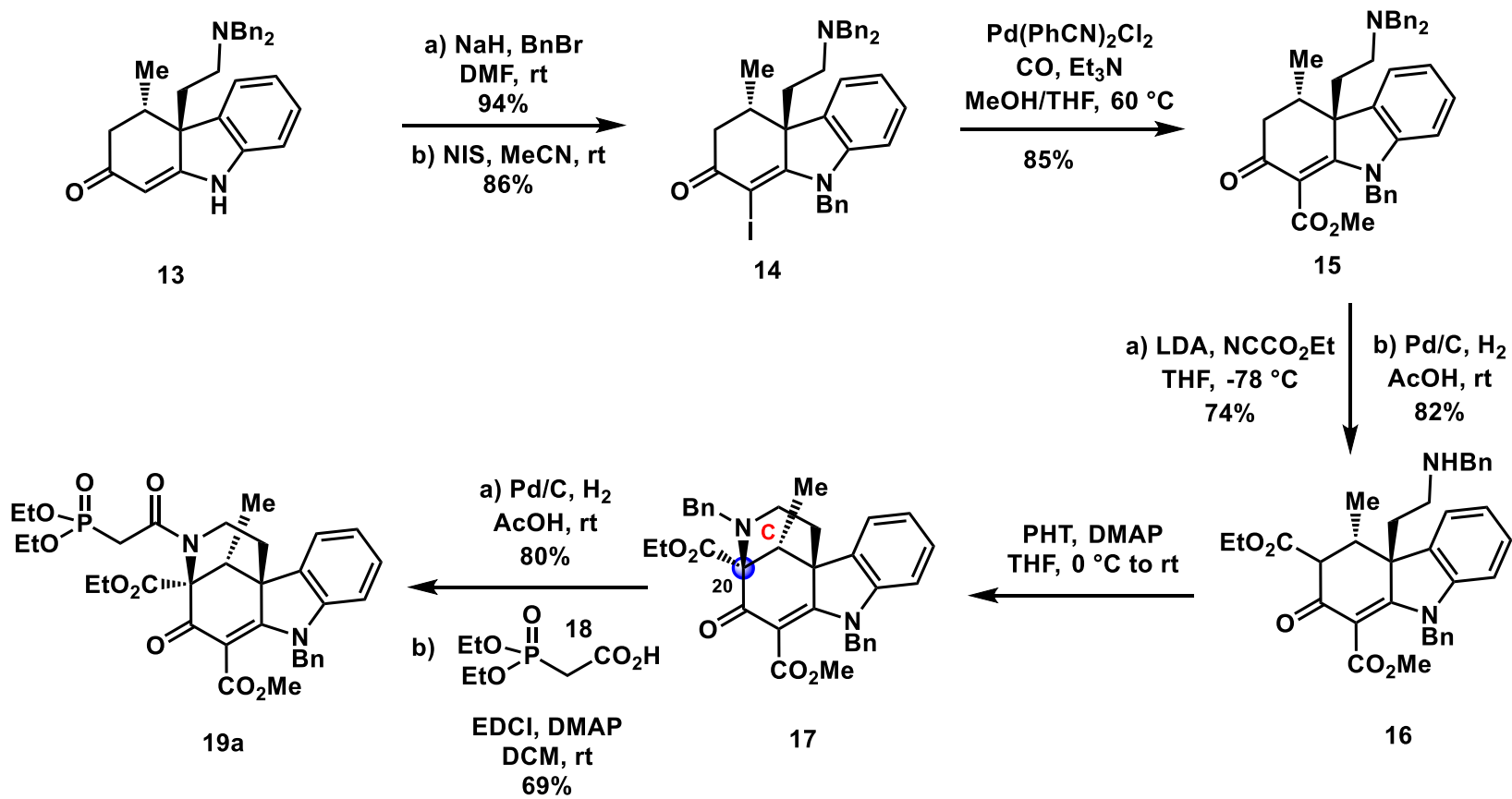
Table 1. Alkylation of Amide 1 Using Et₃O·BF₄

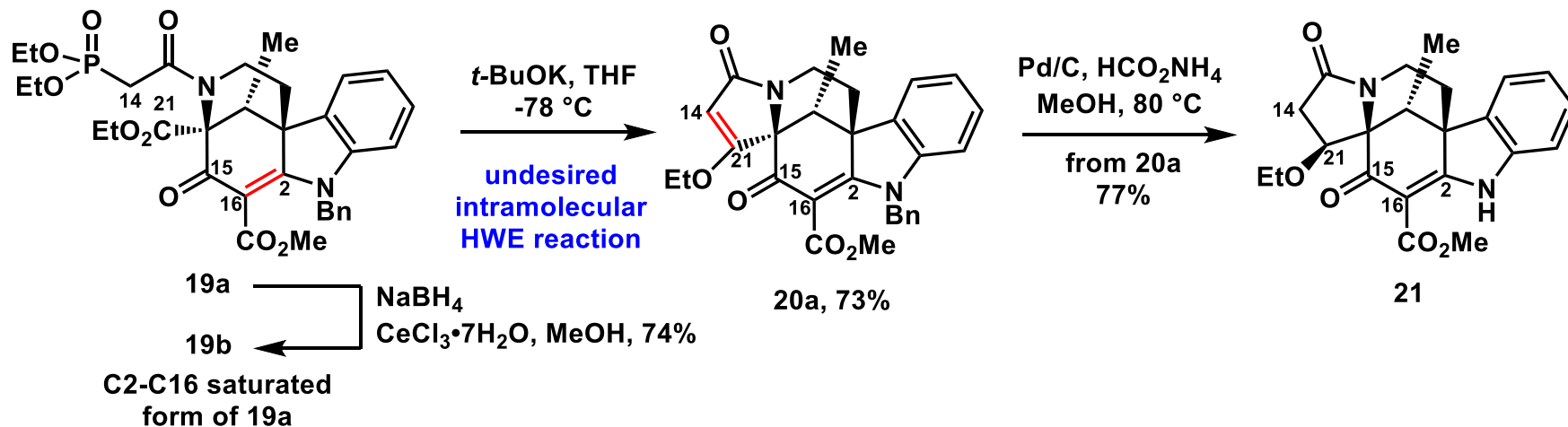


entry	reagents	conditions	ratio 2:3 ^a	yield (2 + 3) (%)
1	Et ₃ O·BF ₄ (2 equiv, fresh batch)	CH ₂ Cl ₂ , rt	65:35	90
2	Et ₃ O·BF ₄ (5 equiv, old batch)	CH ₂ Cl ₂ , rt	90:10	87
3	Et ₃ O·BF ₄ (2 equiv), Et ₃ N (3 equiv)	CH ₂ Cl ₂ , 0 °C → rt	75:25	80
4	Et ₃ O·BF ₄ (2 equiv), <i>i</i> -Pr ₂ EtN (3 equiv)	CH ₂ Cl ₂ , 0 °C → rt	60:40	89
5	Et ₃ O·BF ₄ (2 equiv), DTBMP (3 equiv)	CH ₂ Cl ₂ , 0 °C → rt	85:15	92
6	Et ₃ O·BF ₄ (2 equiv), TFA (10 mol %)	CH ₂ Cl ₂ , rt	100:0	98

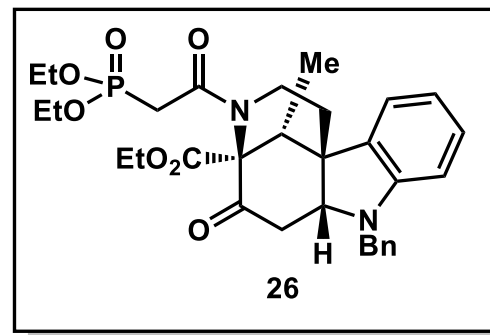
^aDetermined by ¹H NMR spectroscopic analysis of the crude reaction mixture.

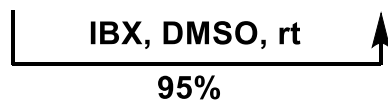
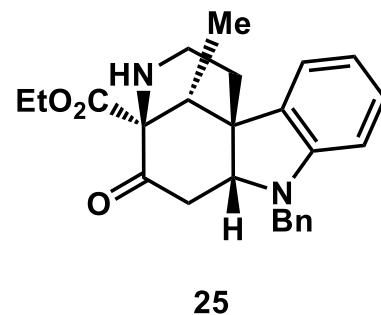
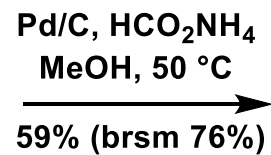
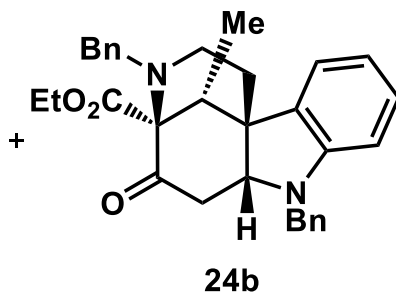
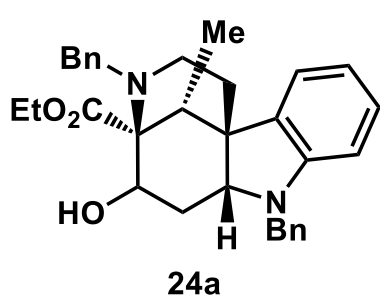
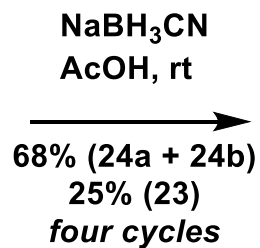
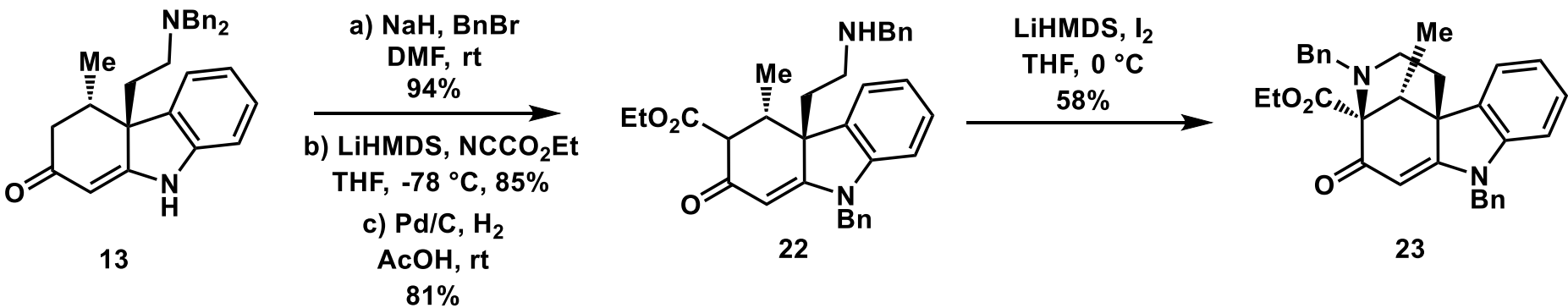
Construction of C Ring (Piperidine Ring)



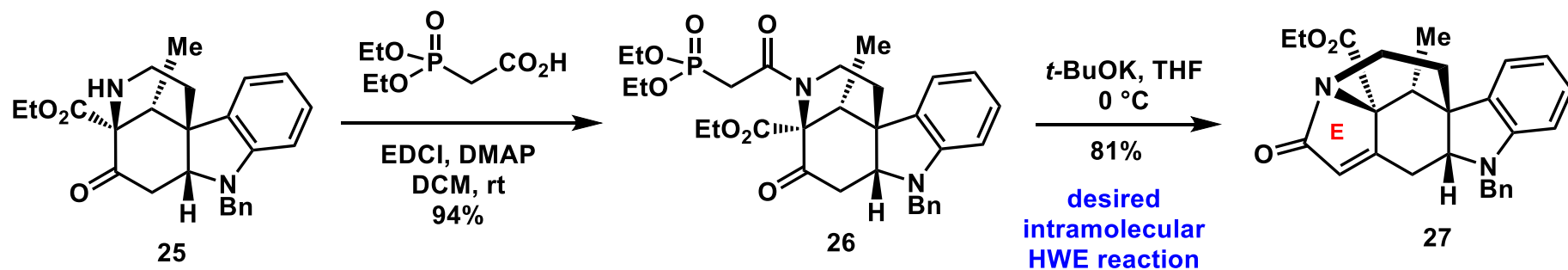


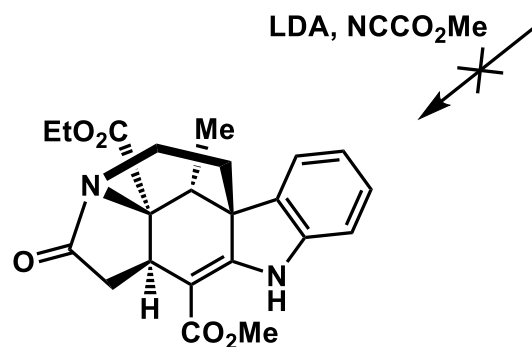
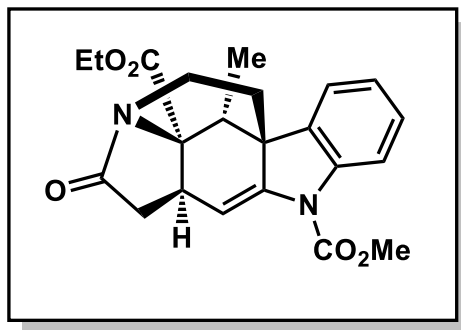
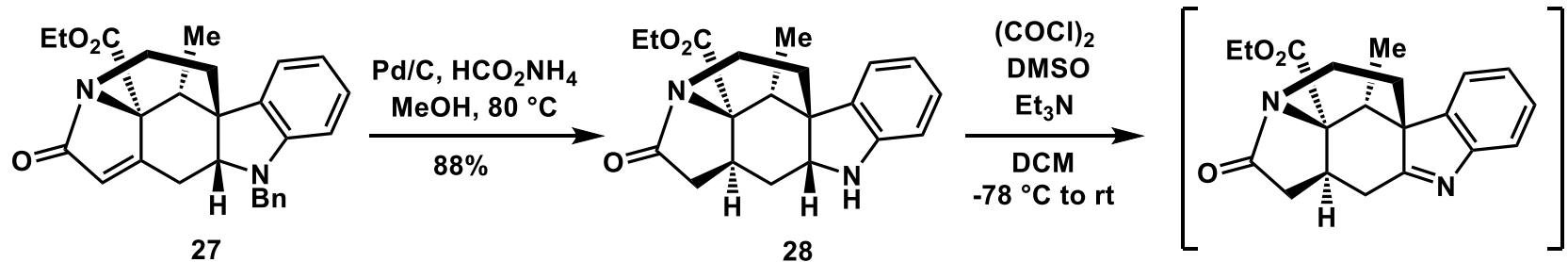
- Inertness of the C15 carbonyl group of vinylogous amide
- The rigidity of the structure imposed by the presence of the double bond



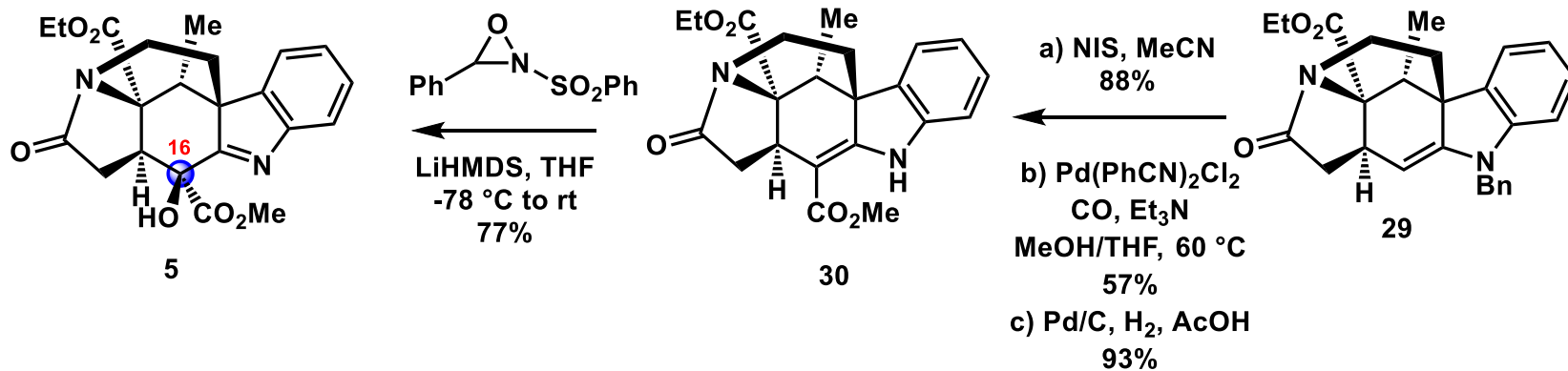


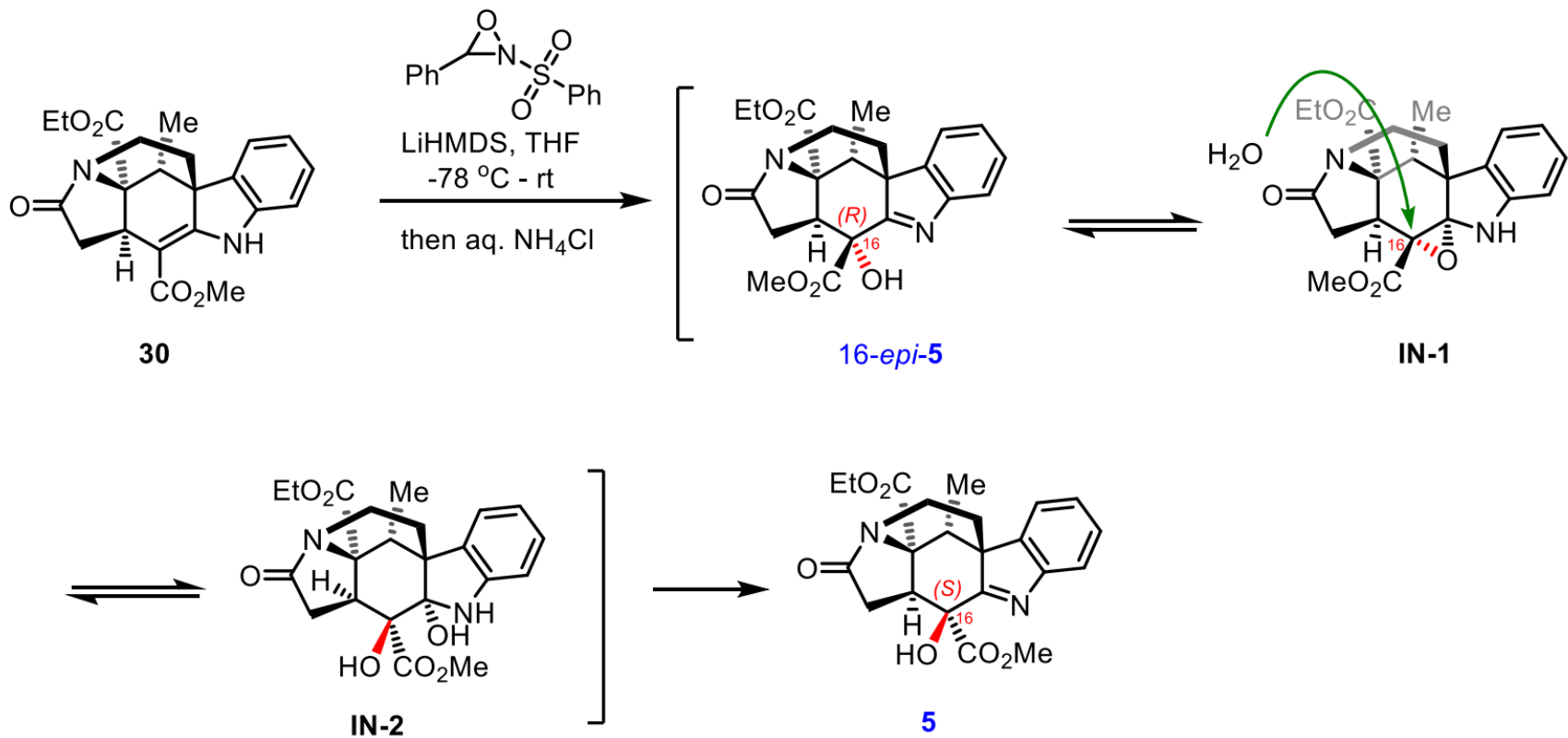
Construction of E Ring (Pyrrolindioe Ring)





then
 NaH, BnBr
 DMF
 45% over 2 steps





Construction of F Ring (Tetrahydrofuran Ring)

