A Review of Total Synthesis of Spirotryprostatin A and B

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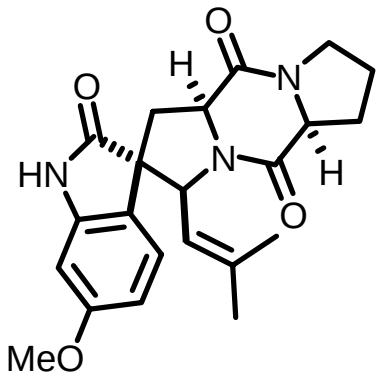
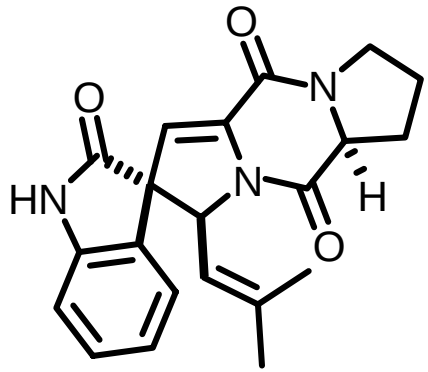
Supergroup meeting
Princeton University
June 28 2006

Novel Mammalian Cell Cycle Inhibitors, Spirotryprostatins A and B



Spirotryprostatin A



Spirotryprostatin B

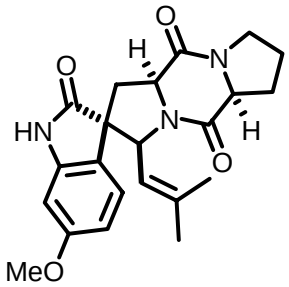
Isolated from the fermentation broth of *Aspergillus fumigatus* BM939 in 1996 by Osada et al.

Both compounds inhibit the mammalian cell cycle in the G2/M phase

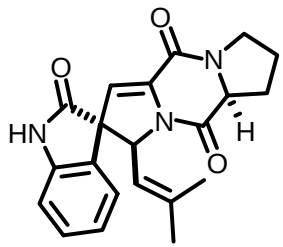
Spirotryprostatin B shows cytotoxic activity on the growth of human leukemia cell line

Osada H. *J. Antibiot*. **1996**,*49*,832
Osada H. *Tetrahedron* **1996**, *52*, 12651

Structure features



Spirotryprostatin A



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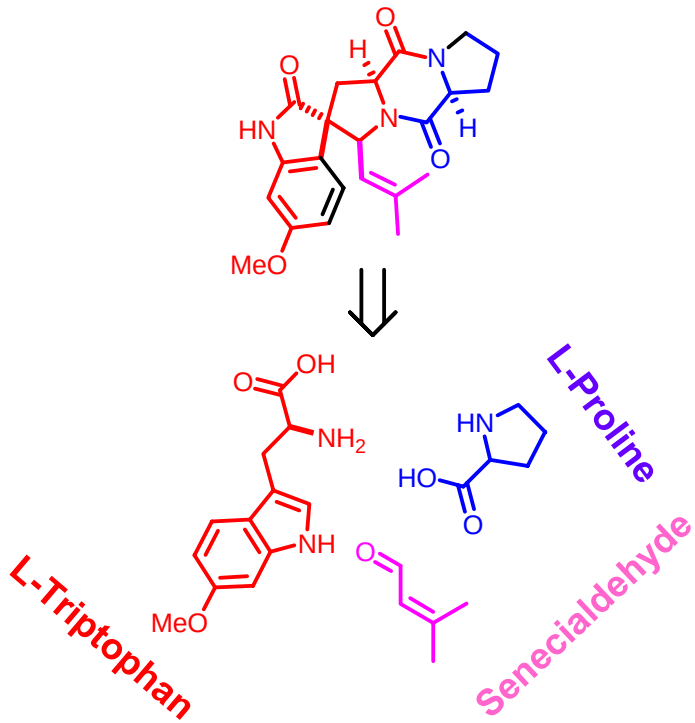


A unique spiro-fusion to a pyrrolidine (dihydro-pyrrole) at the 3-position of the oxindole

The annulated diketopiperazine ring

A prenyl appenage and it's relative stereochemistry with spiro linkage

Key Players

Oxidative spirorearrangement of an indole

----Samuel J. Danishefsky, Spirotryprostatin A

----A. Ganesan, Spirotryprostatin B

Mannich reaction on an oxindole

---- Samuel J. Danishefsky, Spirotryprostatin B

Stereoselective [1,3]-dipolar cycloaddition

----Robert M. Williams, Spirotryprostatin A and B

Asymmetric heck cyclization

----Larry E. Overman, Spirotryprostatin B

Asymmetric nitroolefination

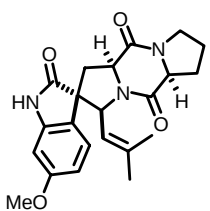
----Kaoru Fuji, Spirotryprostatin B

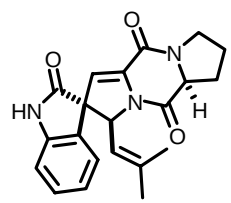
Stereoselective intramolecular N-acyliminium ion spirocyclization

----David A. Horne, Spirotryprostatin A and B

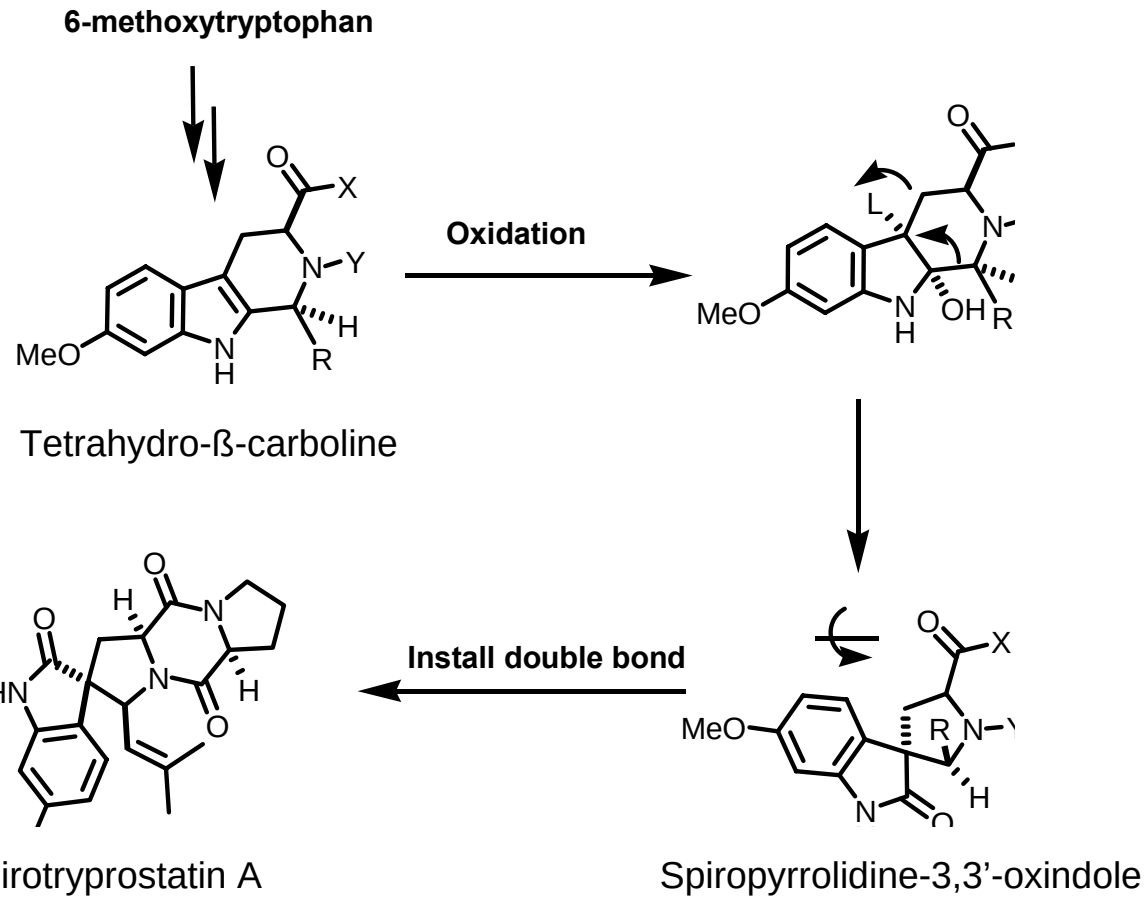
MgI_2-catalyzed ring-expansion reaction

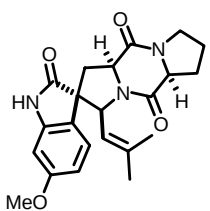
----Erick M. Carreira, Spirotryprostatin B



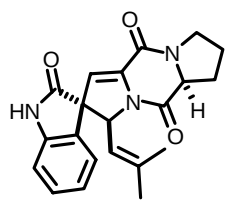


Danishefsky's Synthesis of Spirotryprostatin A

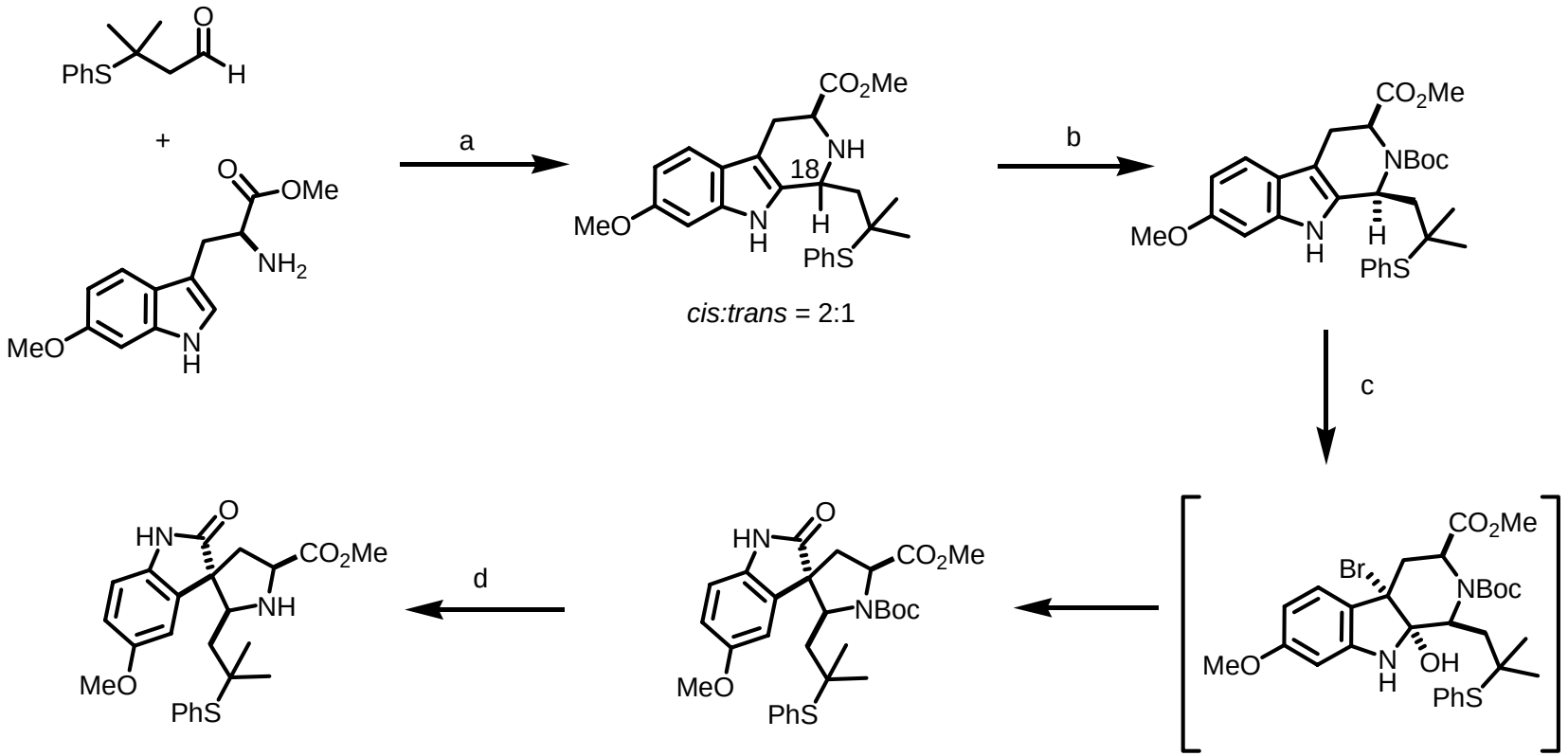




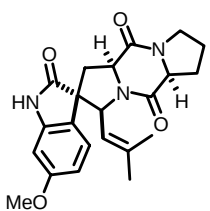
Danishefsky S. J. et al *ACIEE* **1998**, *37*, 1138
Danishefsky S. J. et al *JACS* **1999**, *121*, 2147

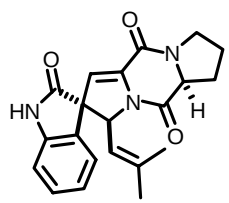


Pictet-Spengler Reaction and Oxidative Rearrangement Build Spiropyrrolidine-3,3'-oxindole

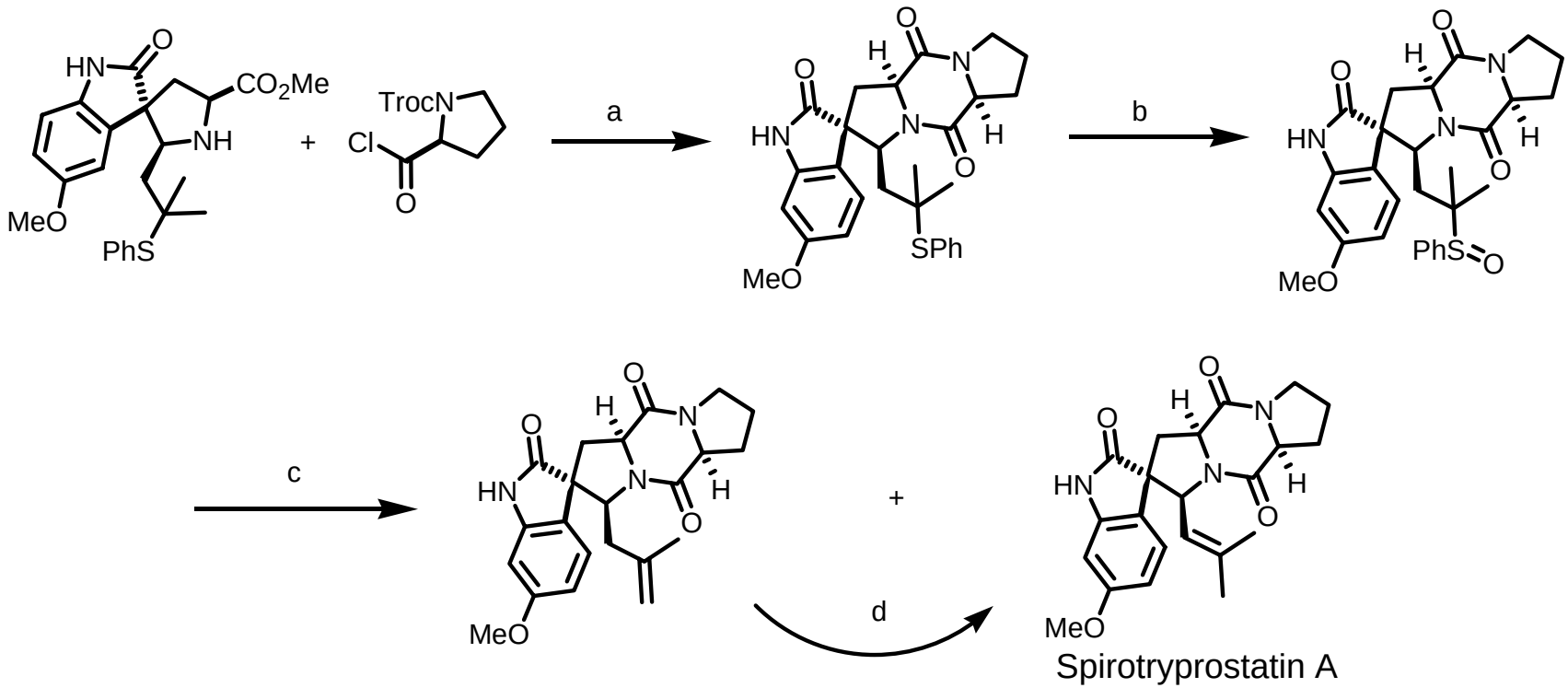


a) CH_2Cl_2 , CF_3CO_2H,molecular sieves (4 Å), 0 °C-20 °C, 88%; b) Boc_2O, CH_3CN, Et_3N, Δ ,84%;c) NBS, THF, H_2O, HOAc, 46%;d) CF_3CO_2H, CH_2Cl_2 , 93%.

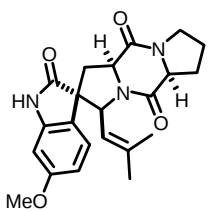


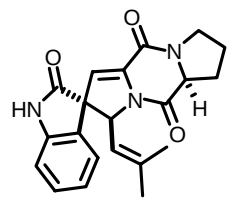


Formation of Diketopiperazine Ring and Complete the Synthesis

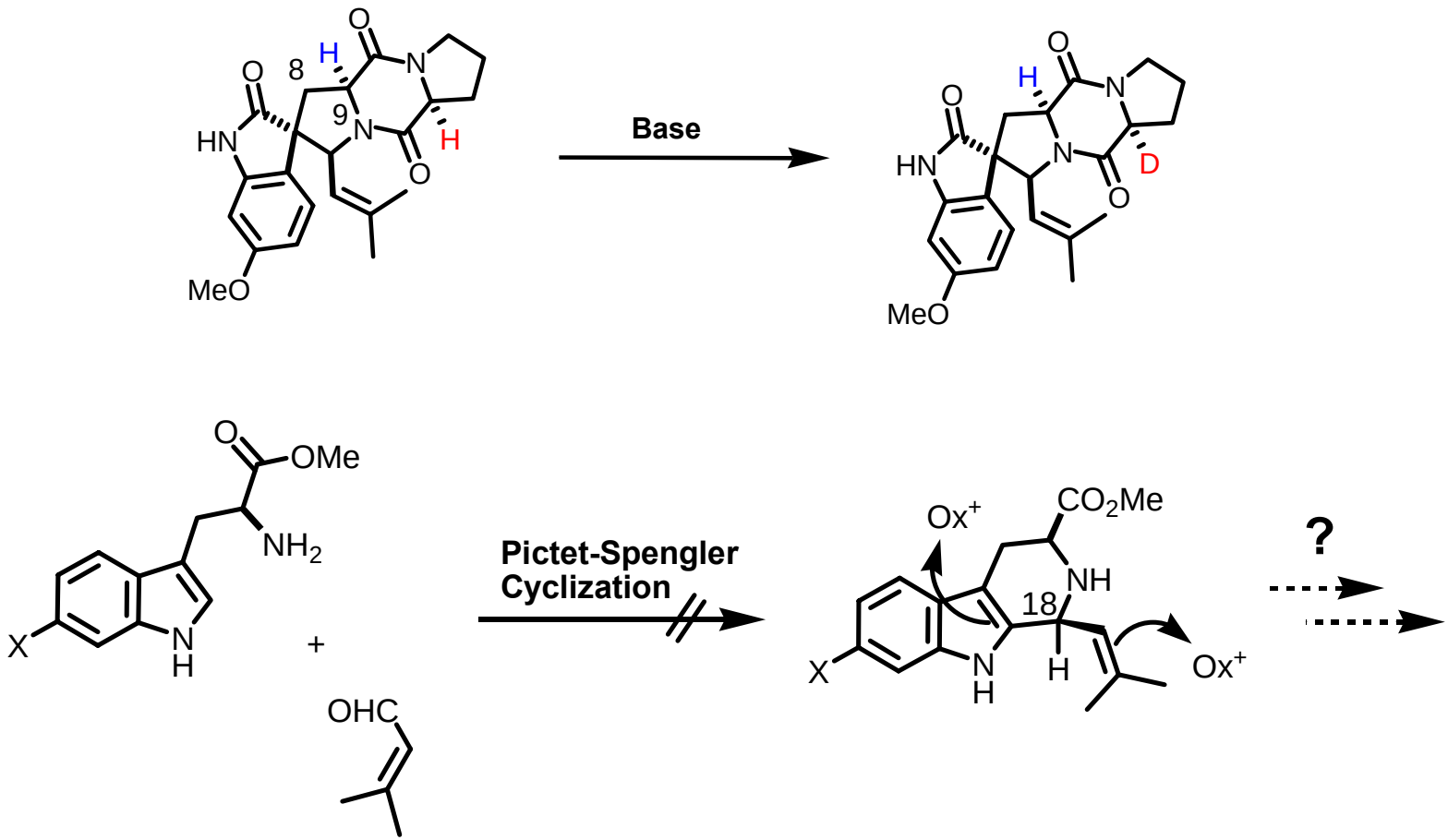


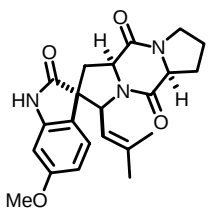
a) CH_2Cl_2 , Et_3N; Zn,NH_4Cl, H_2O, THF, MeOH, 68%; b) $NaIO_4$, H_2O, MeOH; c) $PhCH_3$, Δ, 80% over two steps; d) $RhCl_3 3H_2O$, EtOH, Δ, 41%. Troc:2,2,2-trichloroethoxycarbonyl.



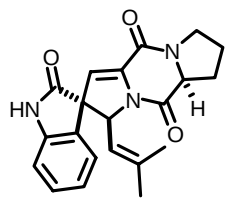


Danishefsky's Synthesis of Spirotryprostatin B

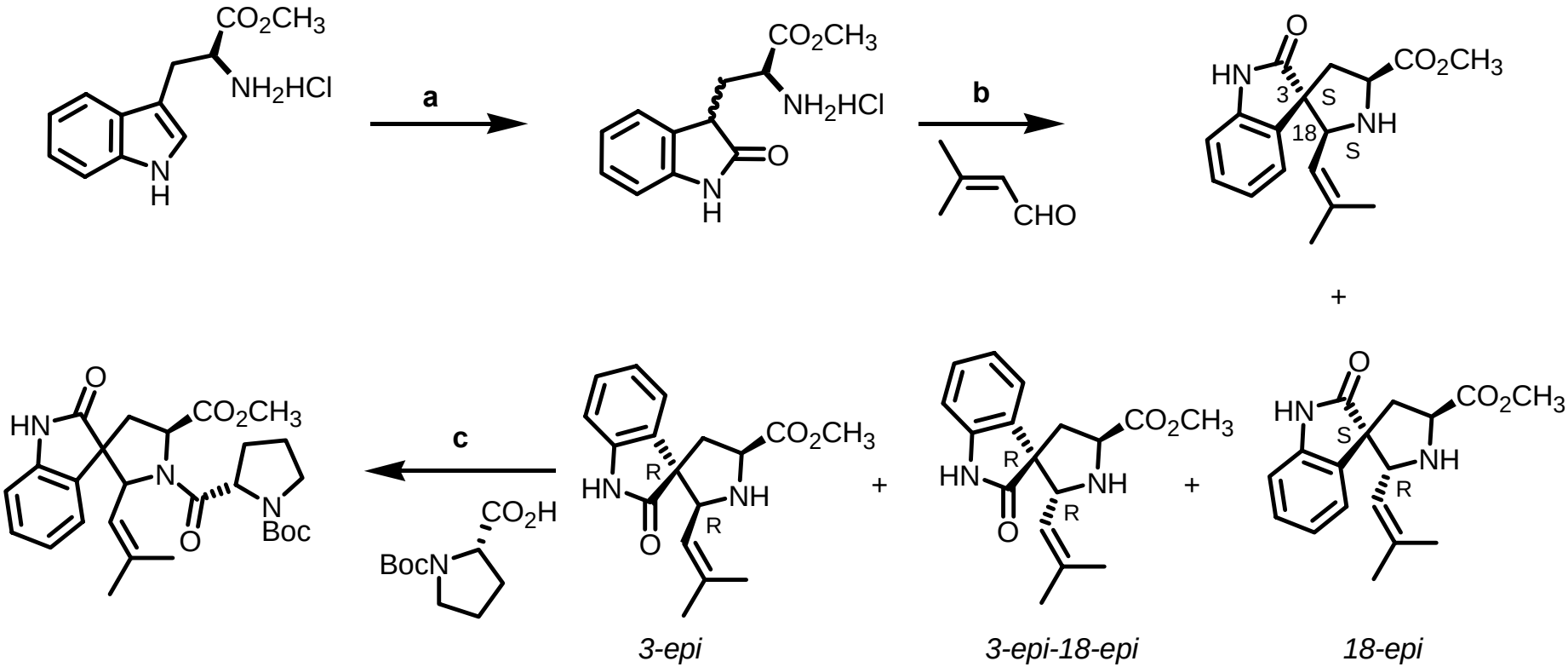




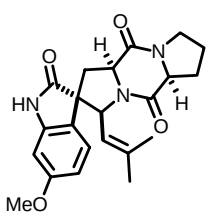
Danishefsky S. J. et al *ACIEE* **2000**, *39*, 2175

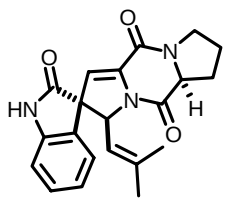


Formation of Spiropyrrolidine-3,3'-oxindole by Mannich Reaction

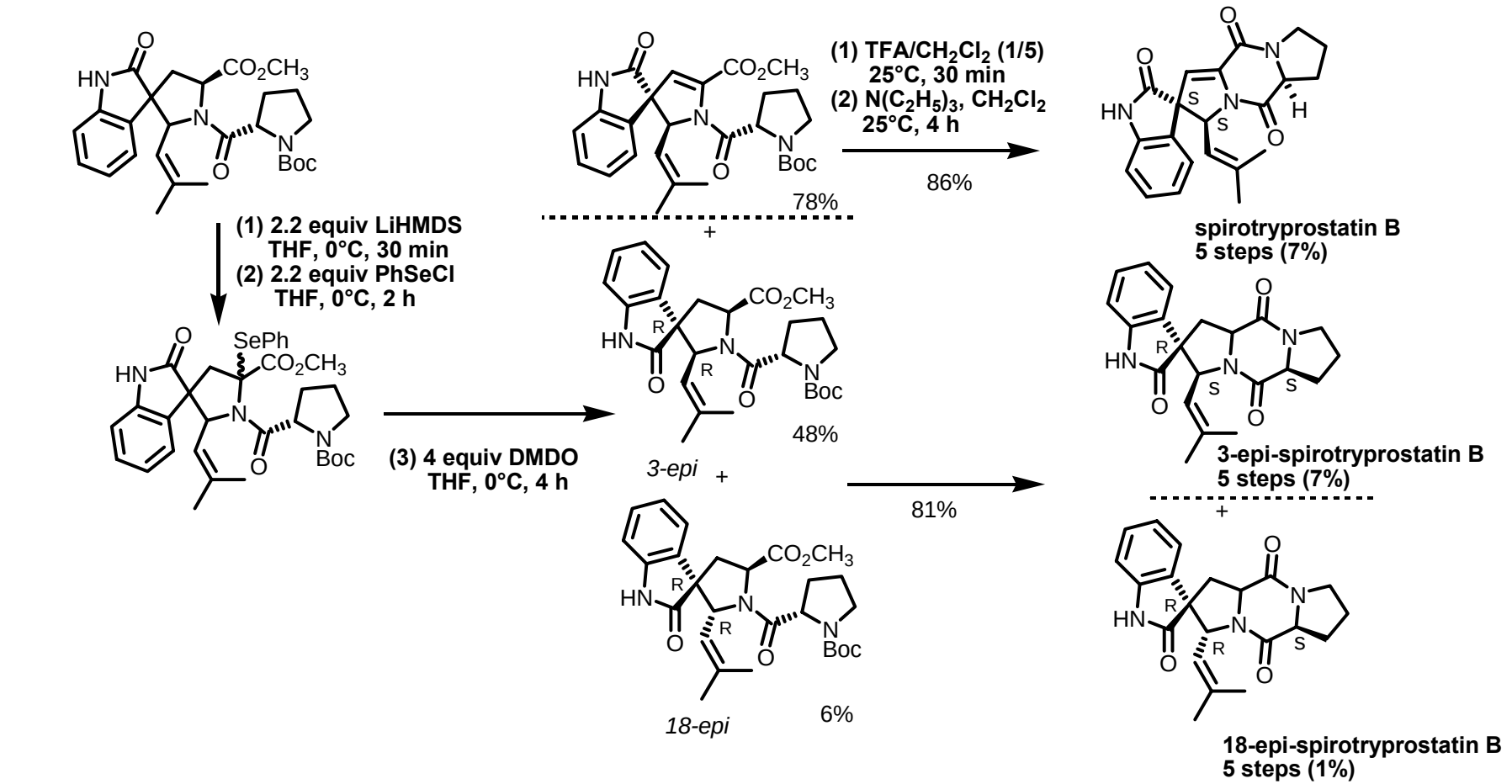


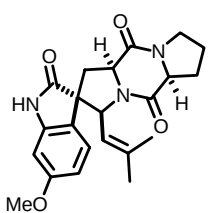
a). 1.05 equiv DMSO, 6 equiv 12 N HCl, AcOH, [5 mol% PhOH],25 °C, 4 h (95%); b). NEt_3 , MS 3 Å, pyridine, 0°C to RT, 9 h; c). 1.2 equiv BOP-Cl, CH_2Cl_2, 2.5 equiv NEt_3, 0°C to 25°C, 2 d, (90%)

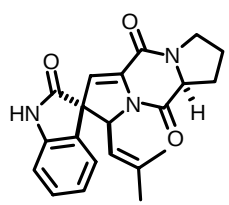




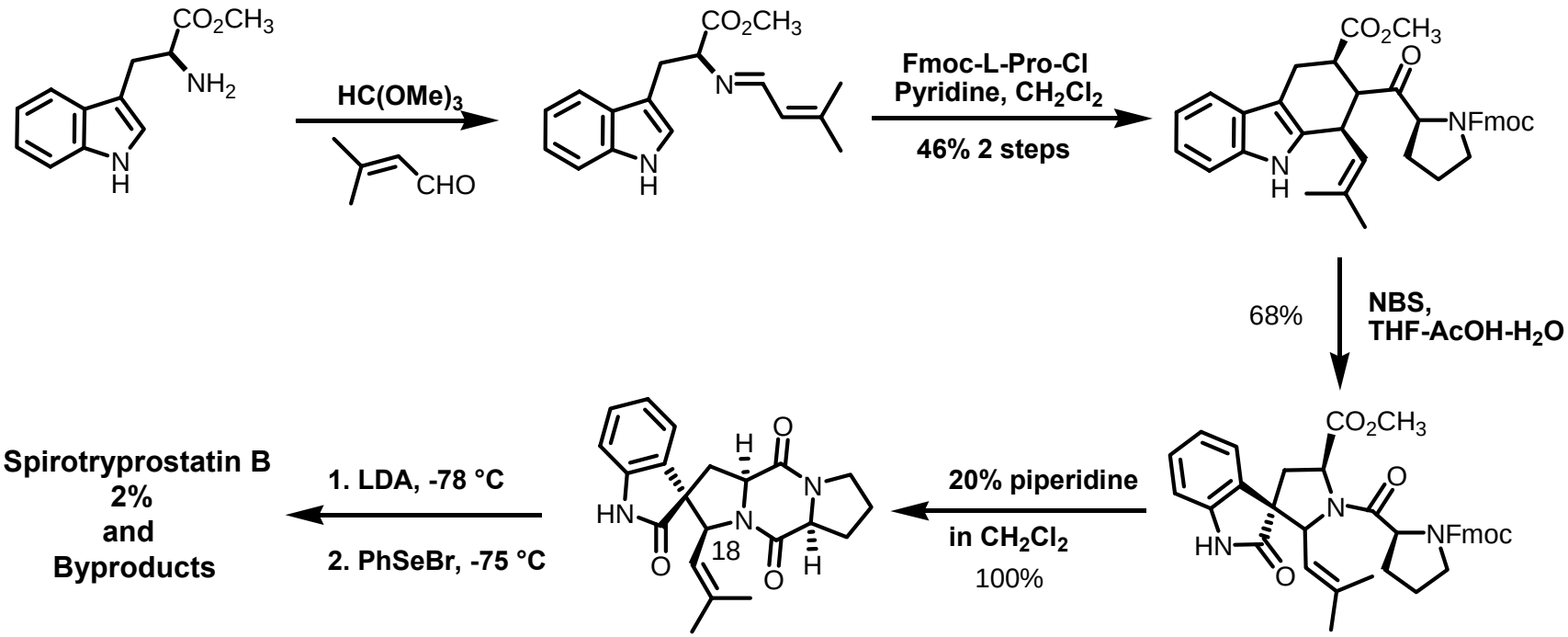
Danishefsky's Synthesis of Spirotryprostatin B

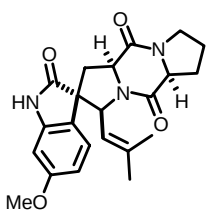




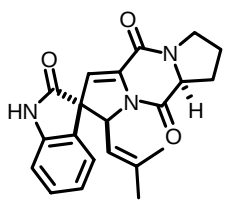


Ganesan's Synthesis of Spirotryprostatin B ---Amazing effect of Proline

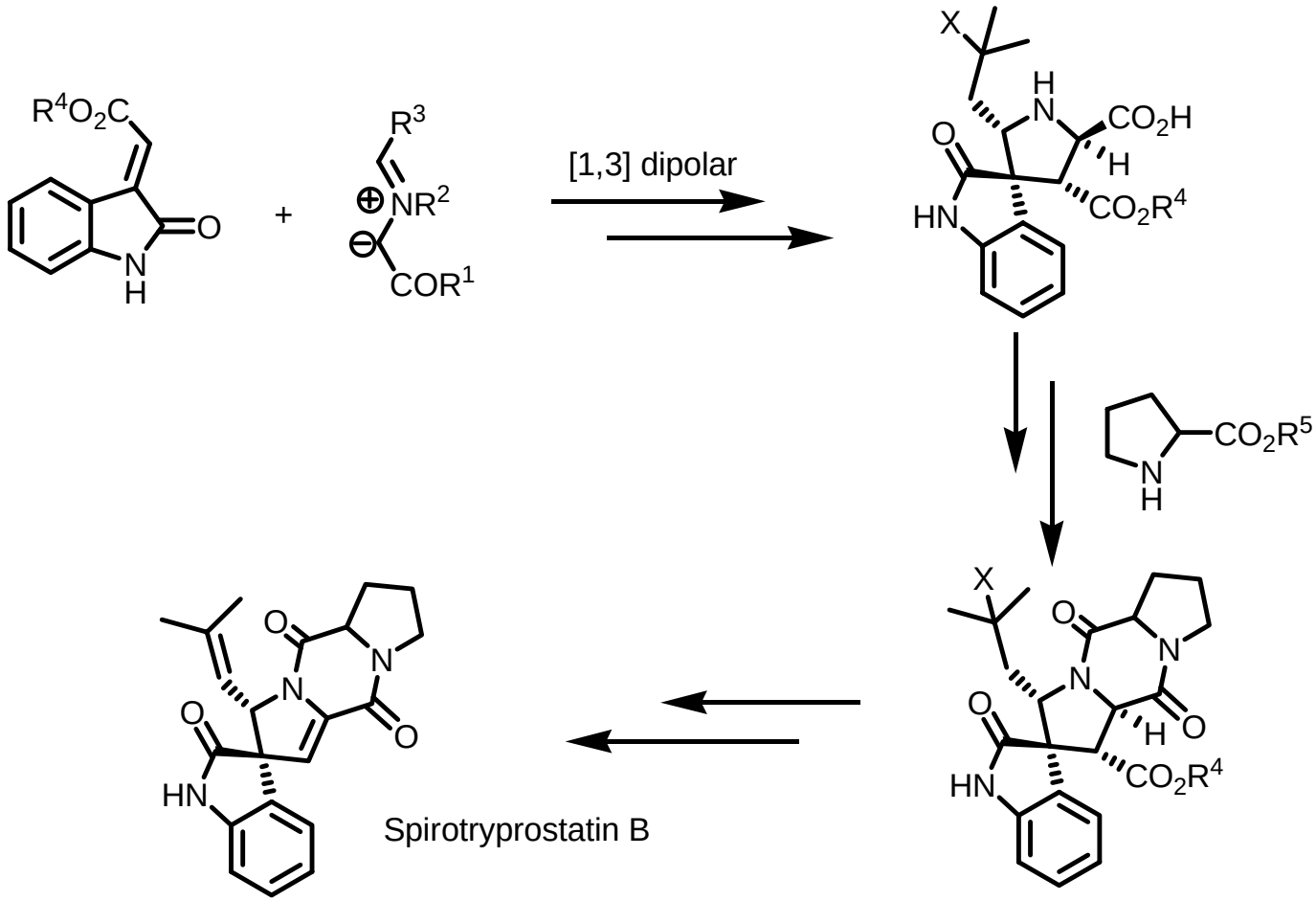


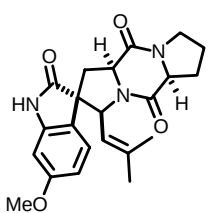


Ganesan A. et al *JOC* **2000**, *65*, 4685

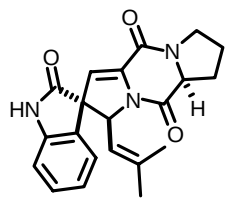


Williams' Synthesis of Spirotryprostatin B

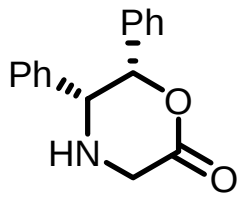




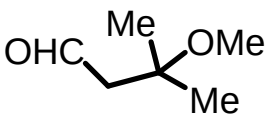
Williams R. M. et al *JACS* **2000**, 122, 5666
Williams R. M. et al *Tetrahedron* **2002**, *58*, 6311



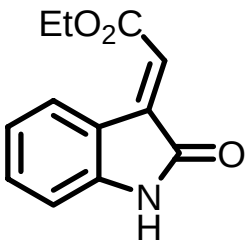
Asymmetric [1,3] Dipolar Cycloaddition Build the Spiropyrrolidine-3,3'-oxindole Core



Diphenylmorpholinone

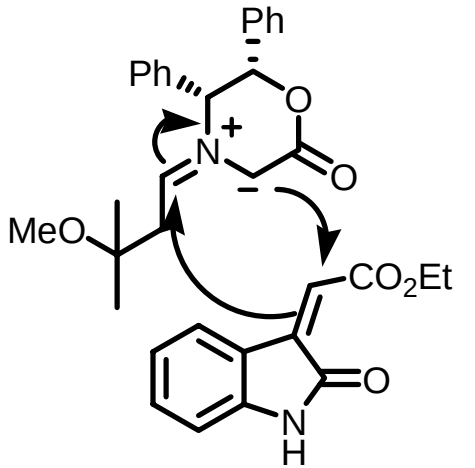


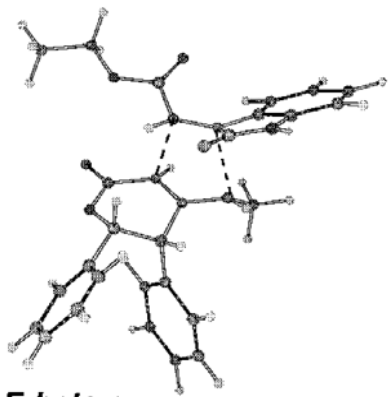
Isovaleraldehyde



Oxindolylideneacetate

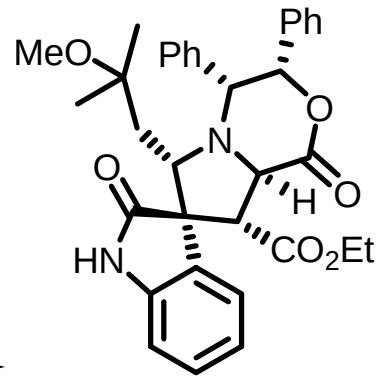
Toluene, MS

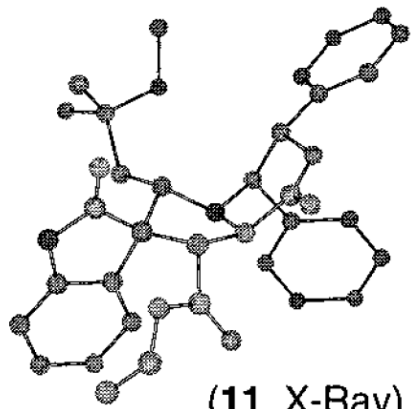




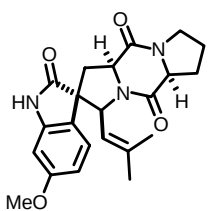
E-beta-exo transition state

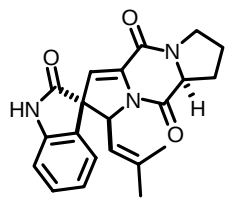
82%



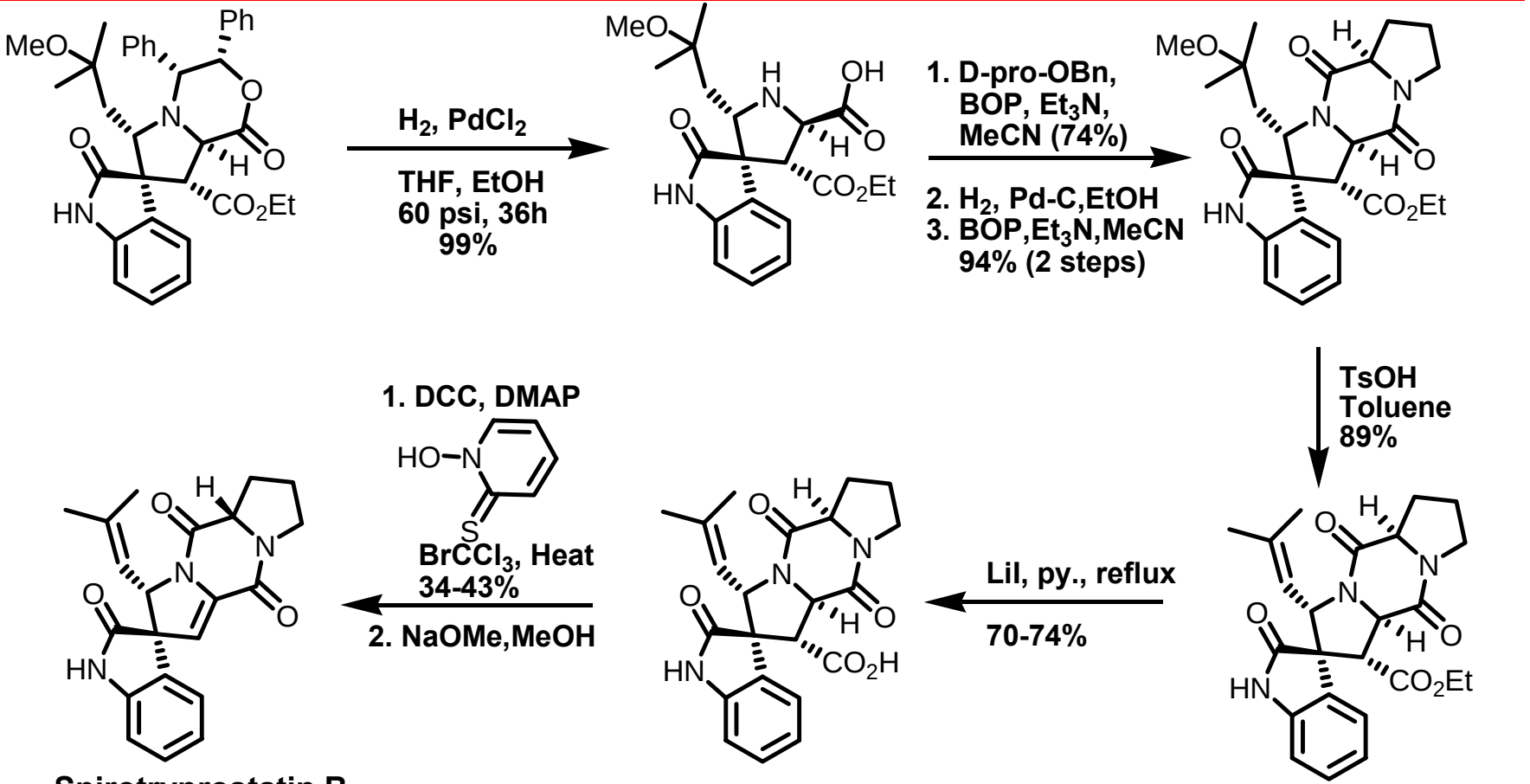


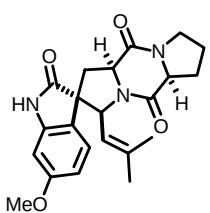
(**11**, X-Ray)

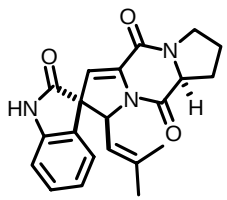




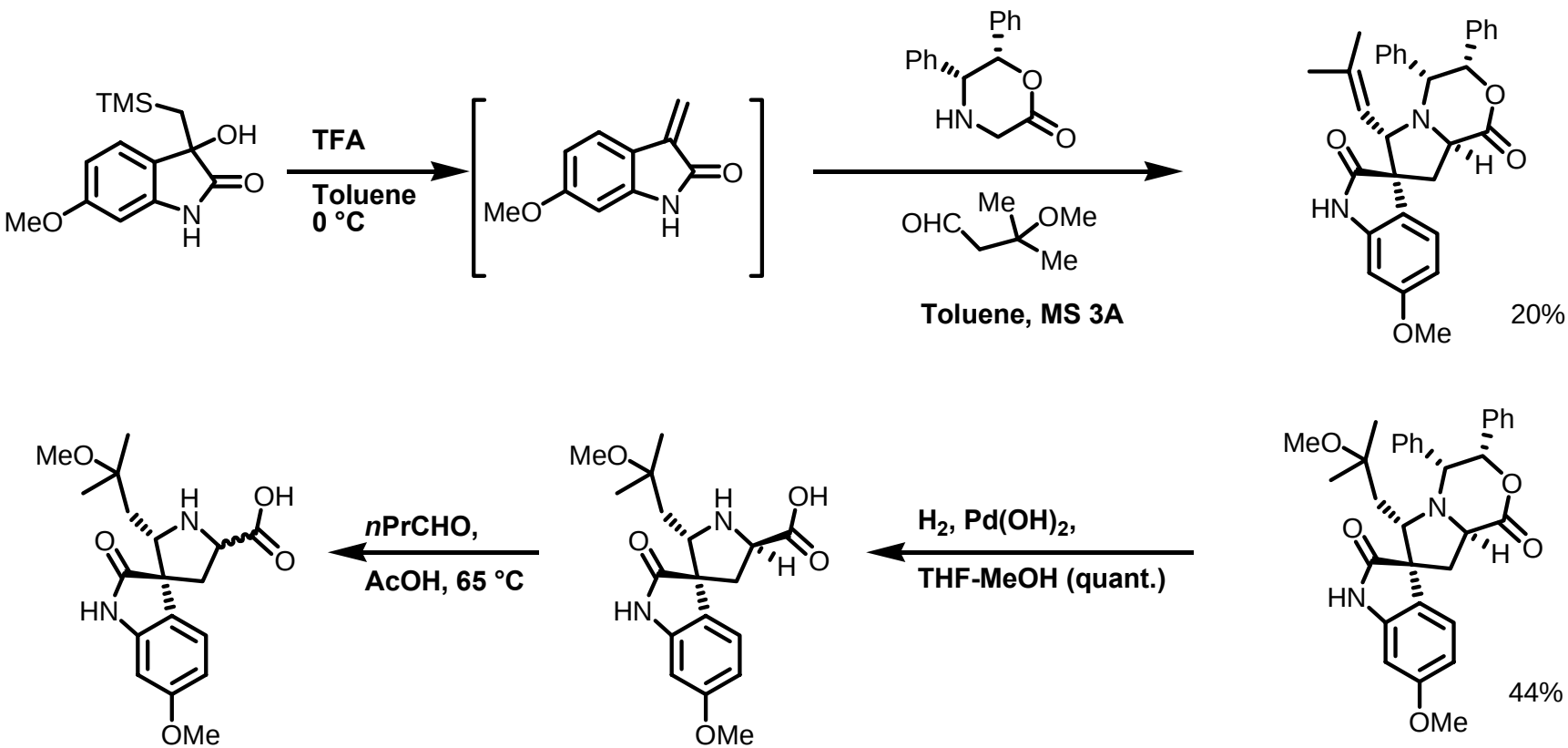
Williams' Synthesis of Spirotryprostatin B

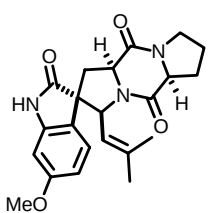




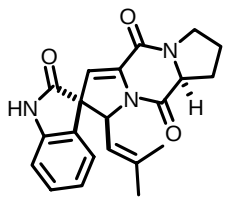


Williams' Synthesis of Spirotryprostatin A

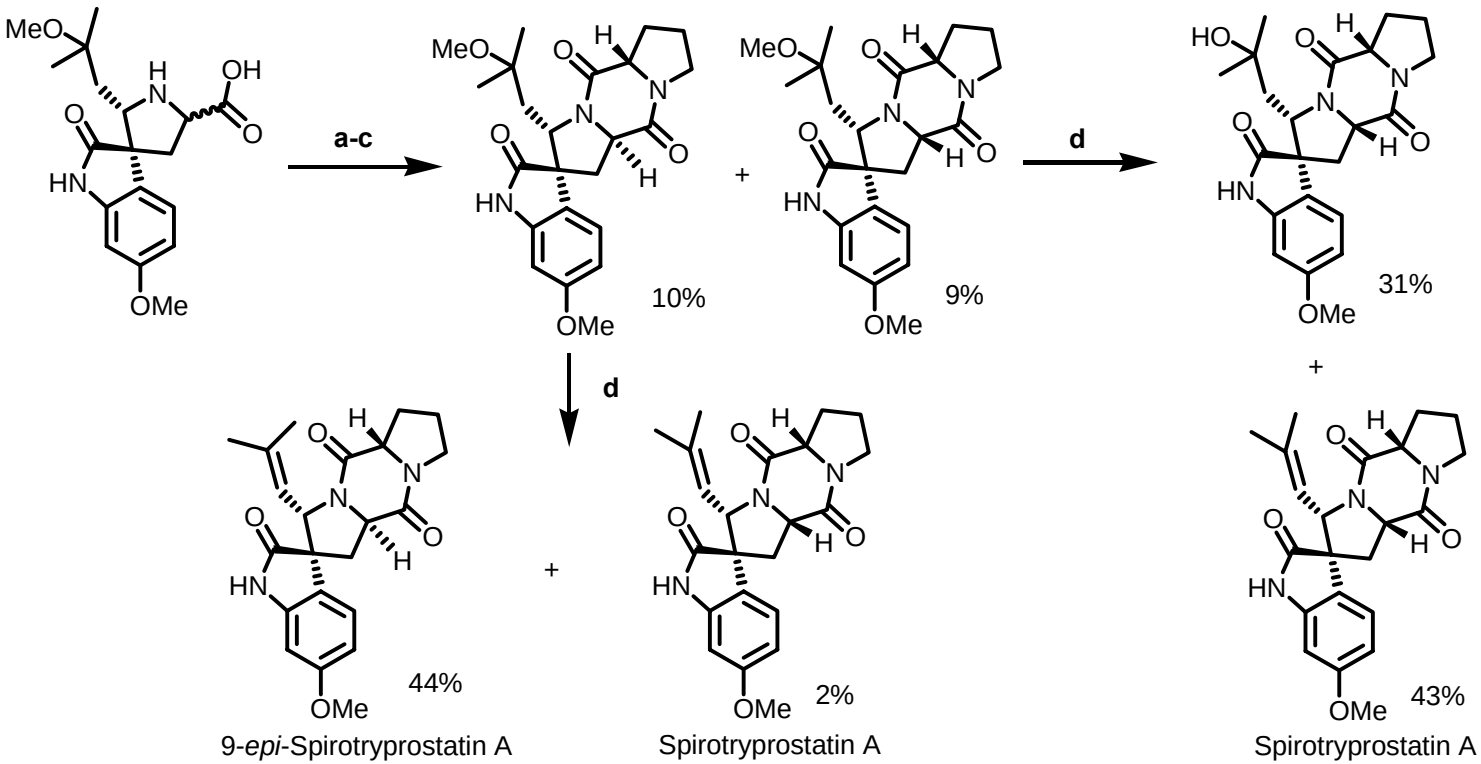




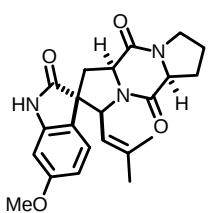
Williams R. M. et al *OL* **2003**, *5*, 3135
Williams R. M. et al *Tetrahedron* **2004**, *60*, 9503

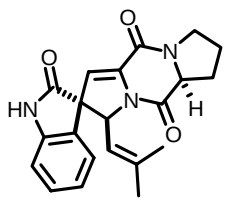


Williams' Synthesis of Spirotryprostatin A

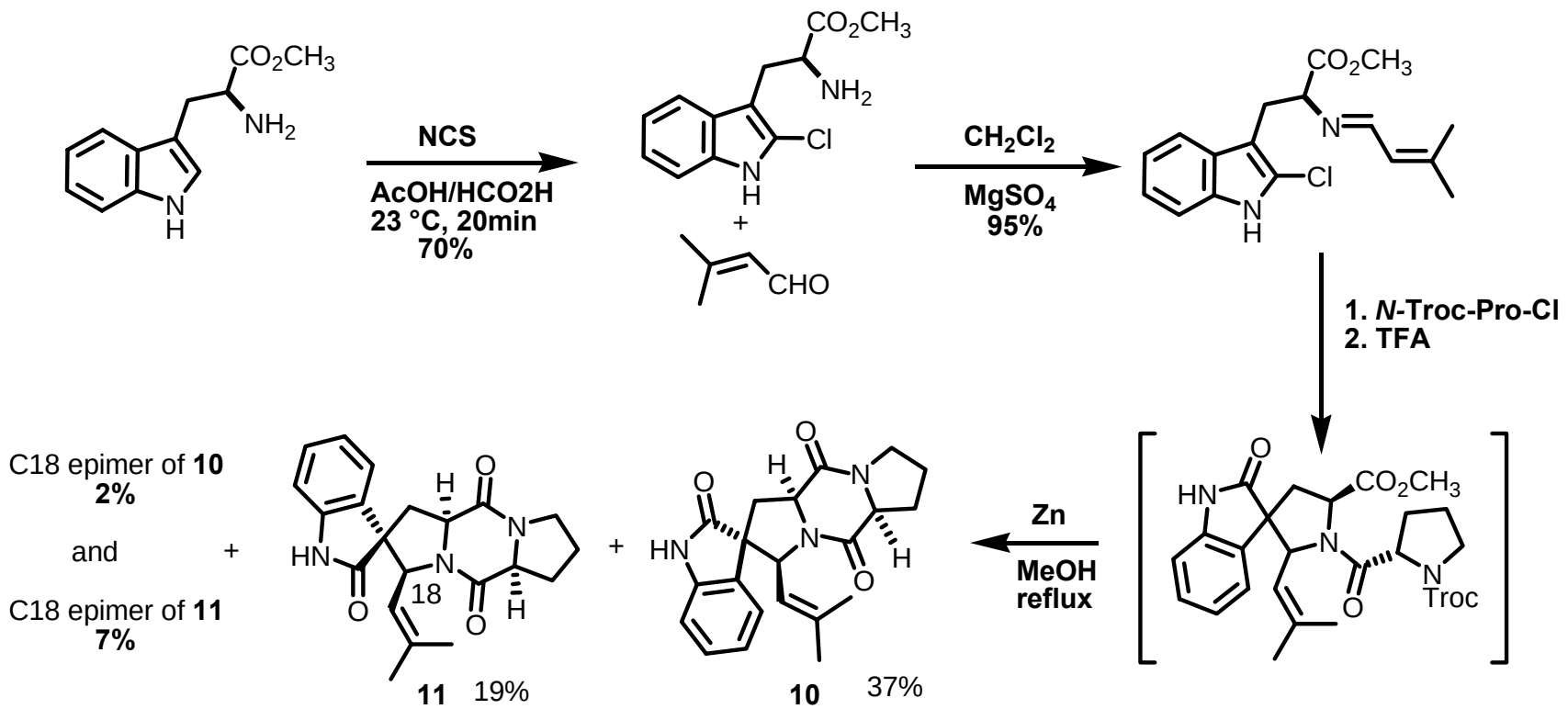


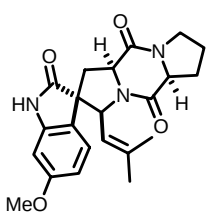
(a) L-Pro-OBn HCl, BOP, Et_3N, MeCN;(b) H_2, Pd/C, EtOH-MeOH; (c) WSC, Et3N, MeCN; (d) *p*-TsOH,H_2O, 3 Å sieves, toluene, 110 °C. Abbreviations: BOP=benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate; WSC= 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride



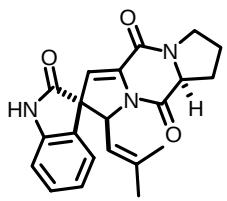


Horne's Synthesis of Spirotryprostatin B ---Spirocylization Induced by Acyliminium

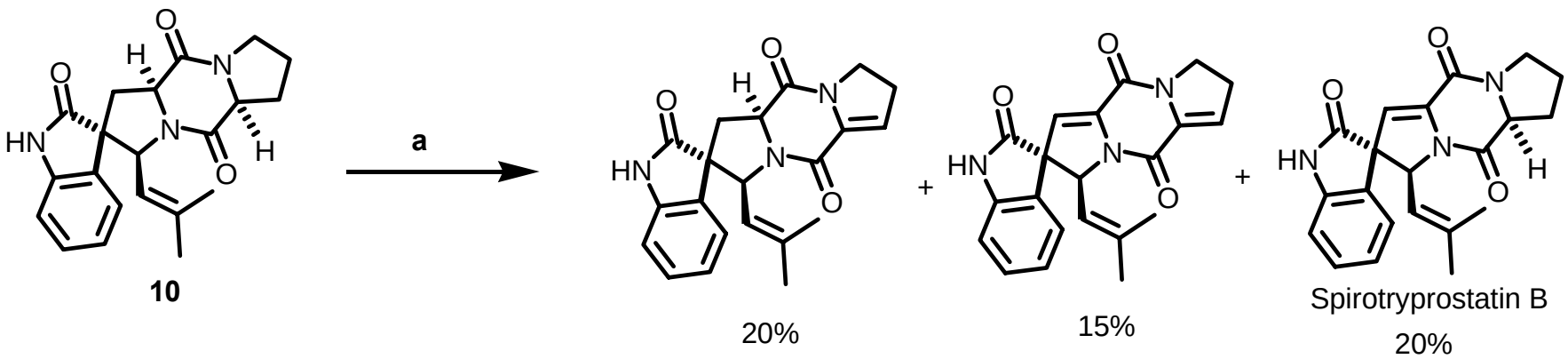




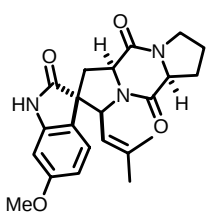
Horne D. A. et al *ACIEE* **2004**, *43*, 5357

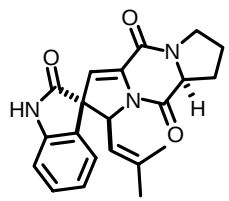


Horne's Synthesis of Spirotryprostatin B

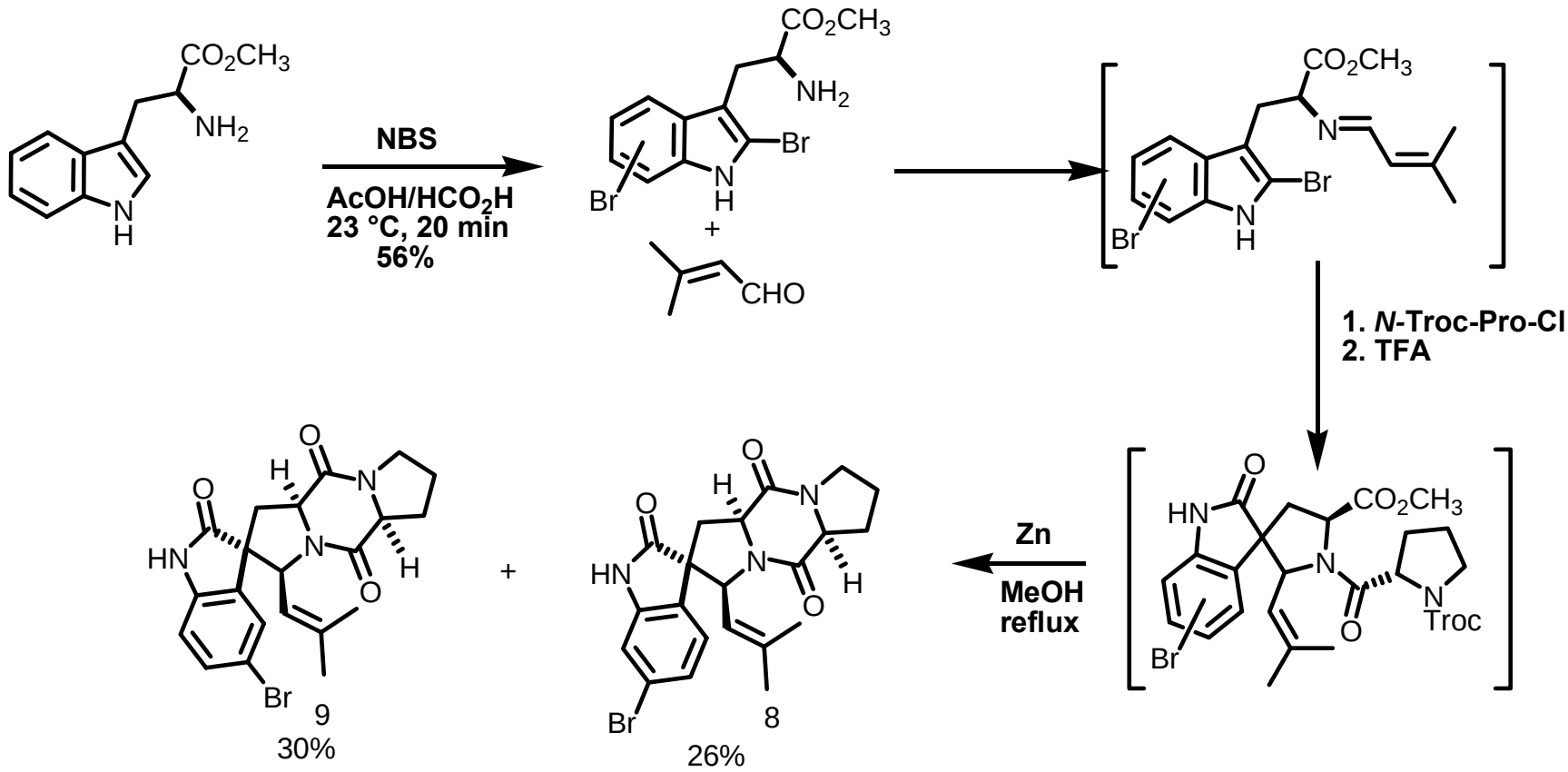


a) LiHMDS(3 equiv),THF, 0°C, 30 min; then PhSeCl (3 equiv), 3 h, 0°C; then PhSeCl (3 equiv), 23°C, 16 h.





Horne's Synthesis of Spirotryprostatin A



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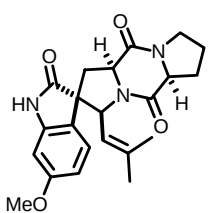
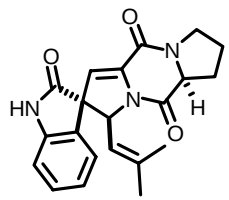
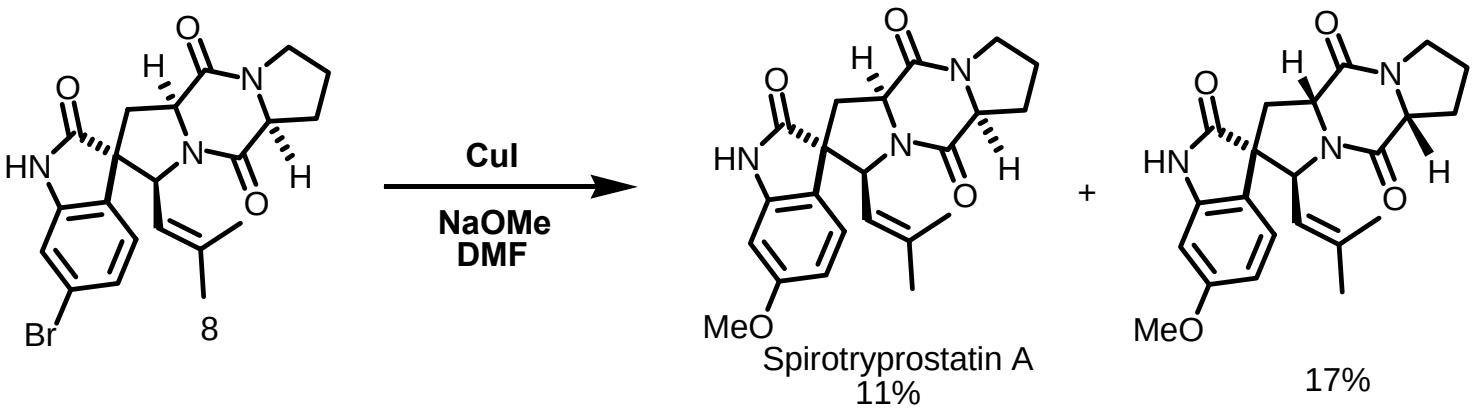
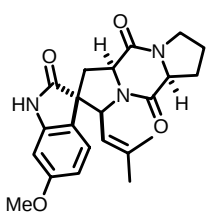
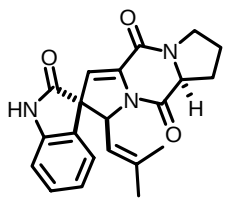




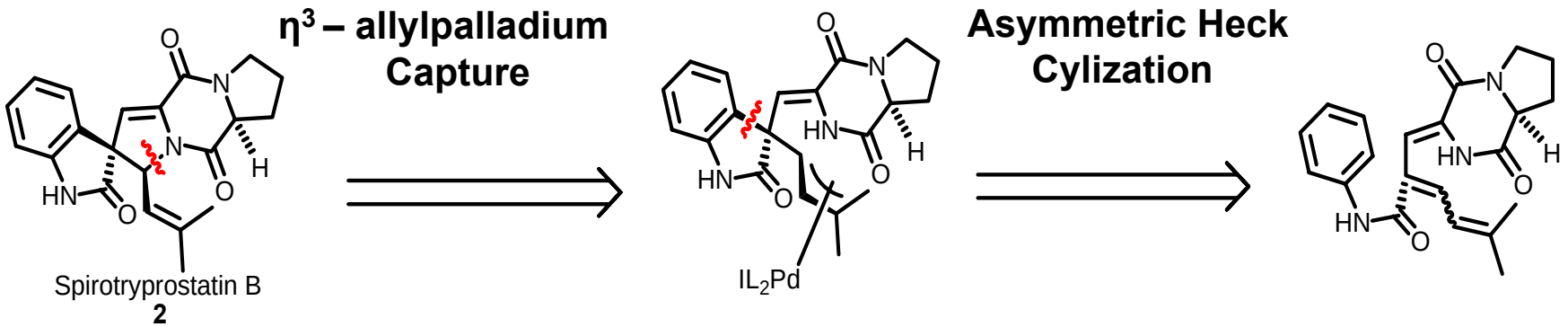
Horne's Synthesis of Spirotryprostatin A

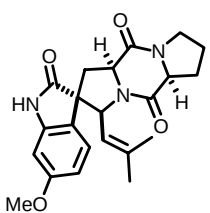






Overman's Synthesis of Spirotryprostatin B





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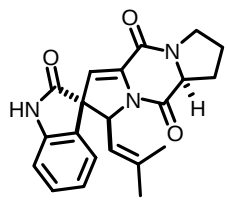
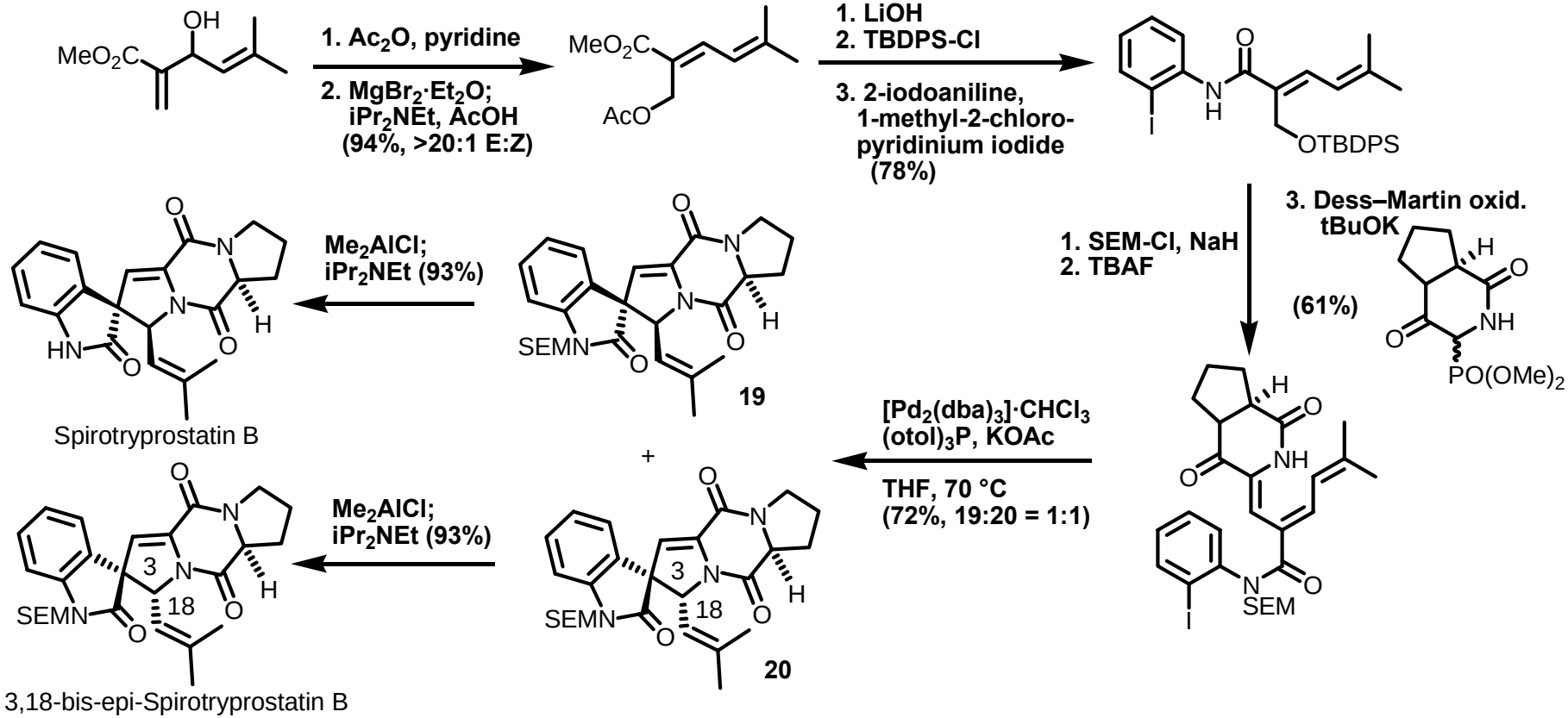
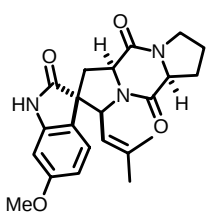
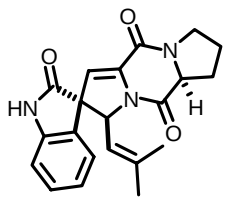


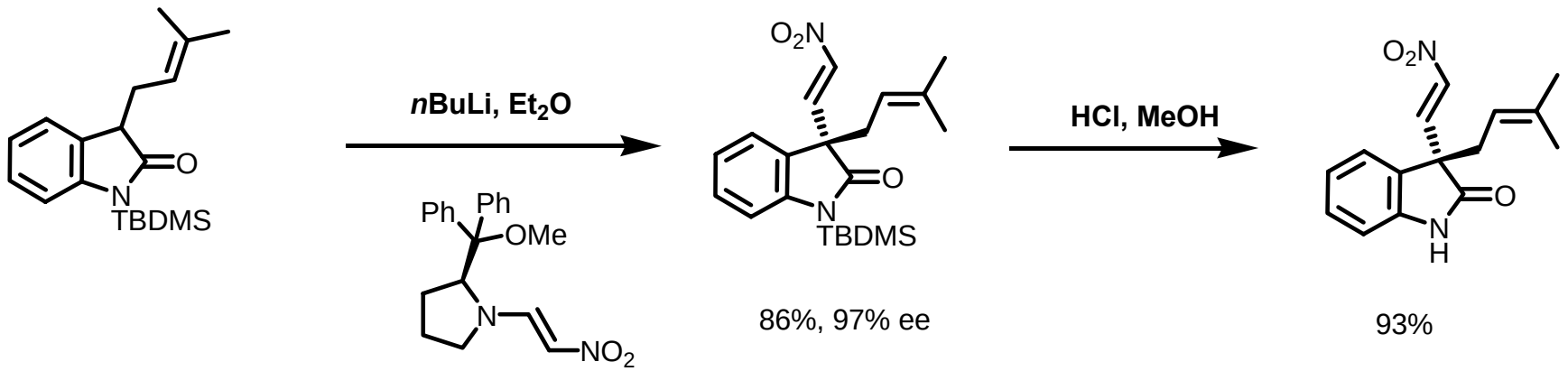
Overman's Synthesis of Spirotryprostatin B

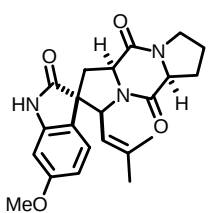




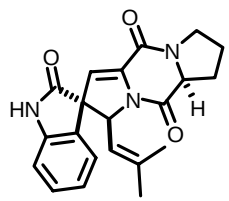


Fuji's Synthesis of Spirotryprostatin B

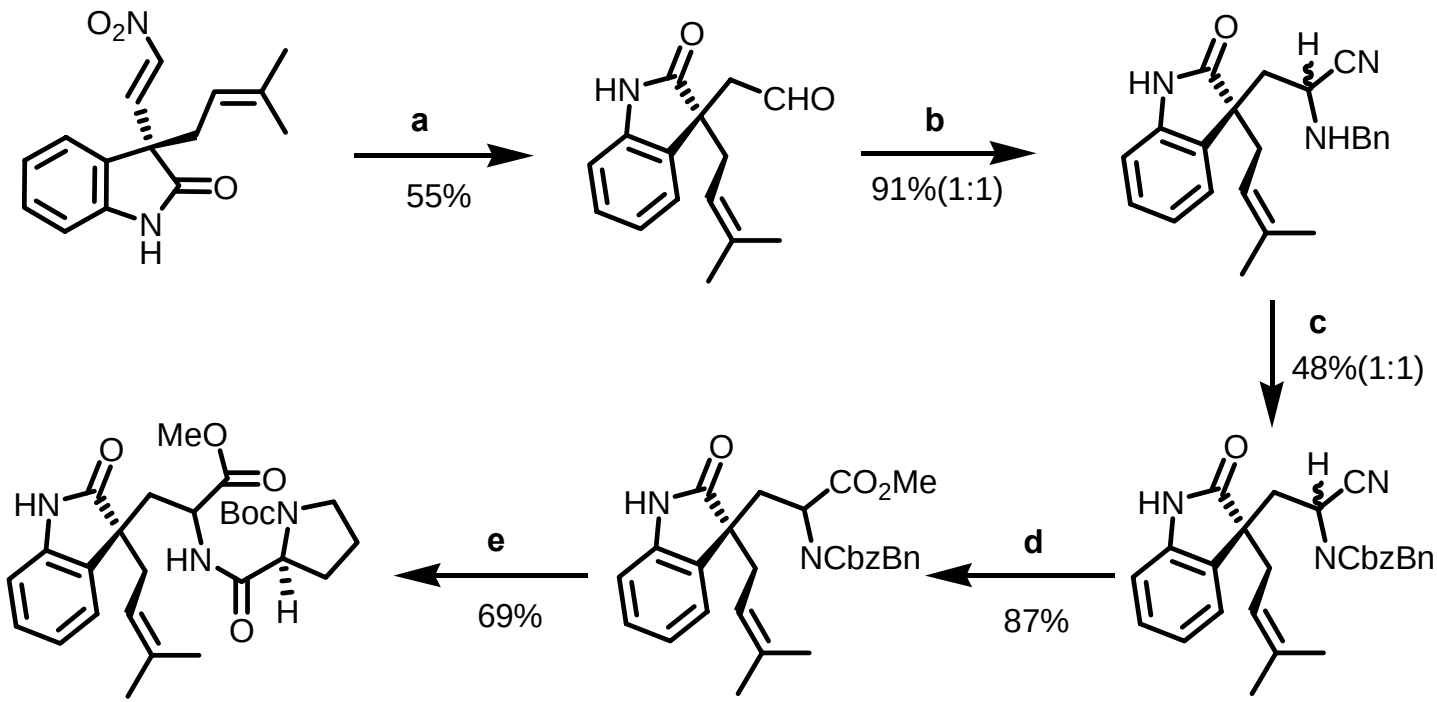




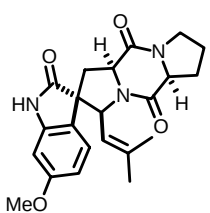
Fuji K. et al *Synlett* **1995**, 367



Fuji's Synthesis of Spirotryprostatin B



a) $TiCl_3$ (20% aqueous, 5.0 equiv), NH_4OAc (5.0 equiv),MeOH:H_2O (4:1), rt, 3 h; b) i. $BnNH_2$ (1.0 equiv), DCM, rt, 3 h;ii. TMSCN (1.05 equiv), rt, 3 h; c) CbzCl (1.2 equiv), Et_3N (2.4 equiv), DCM, rt, 12 h; (d) i. K_2CO_3, MeOH, rt, 6 h; ii. aqueous 1M HCl, rt, 0.5 h; (e) i. Pd black (80 wt %), 5% HCO_2H in MeOH,20 min; ii. *N*-Boc-L-prolide (1.1 equiv), WSC (1.2 equiv), DMC,12 h



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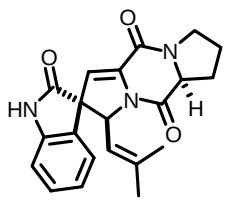
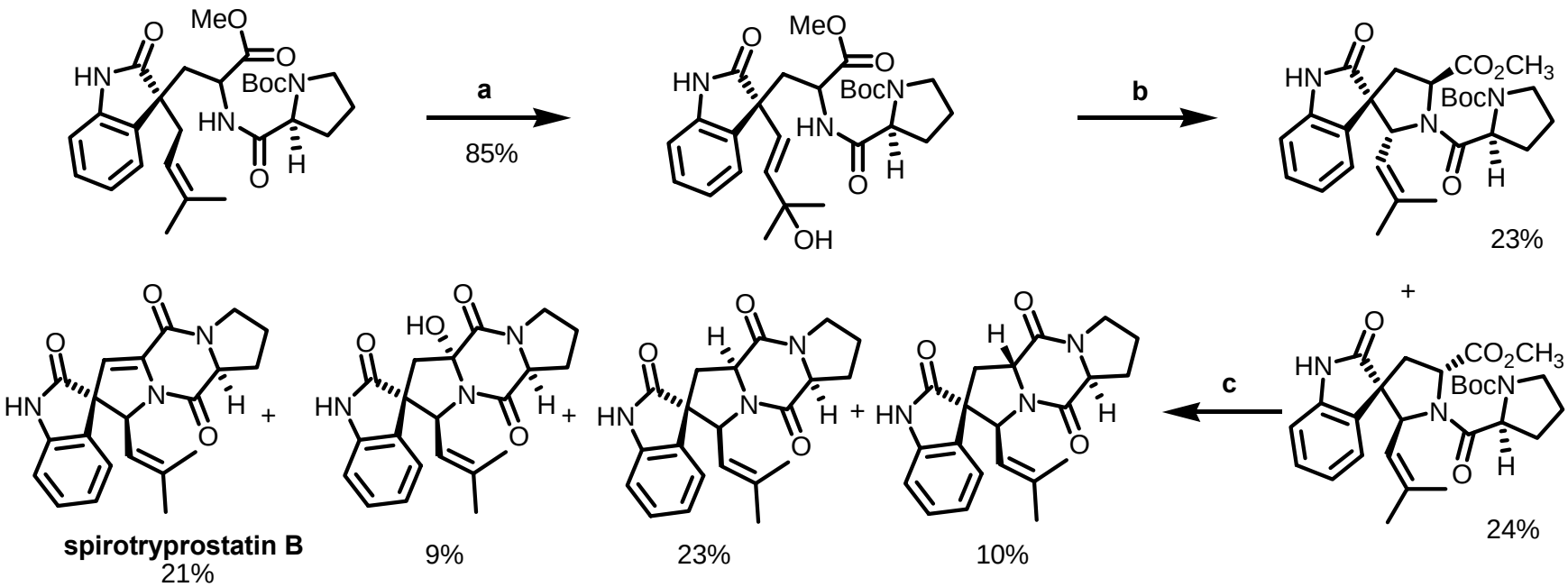
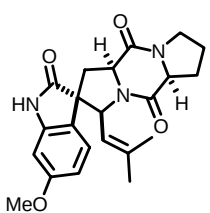
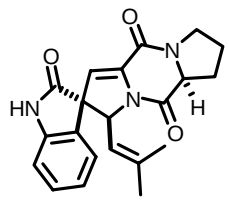


Fuji's Synthesis of Spirotryprostatin B

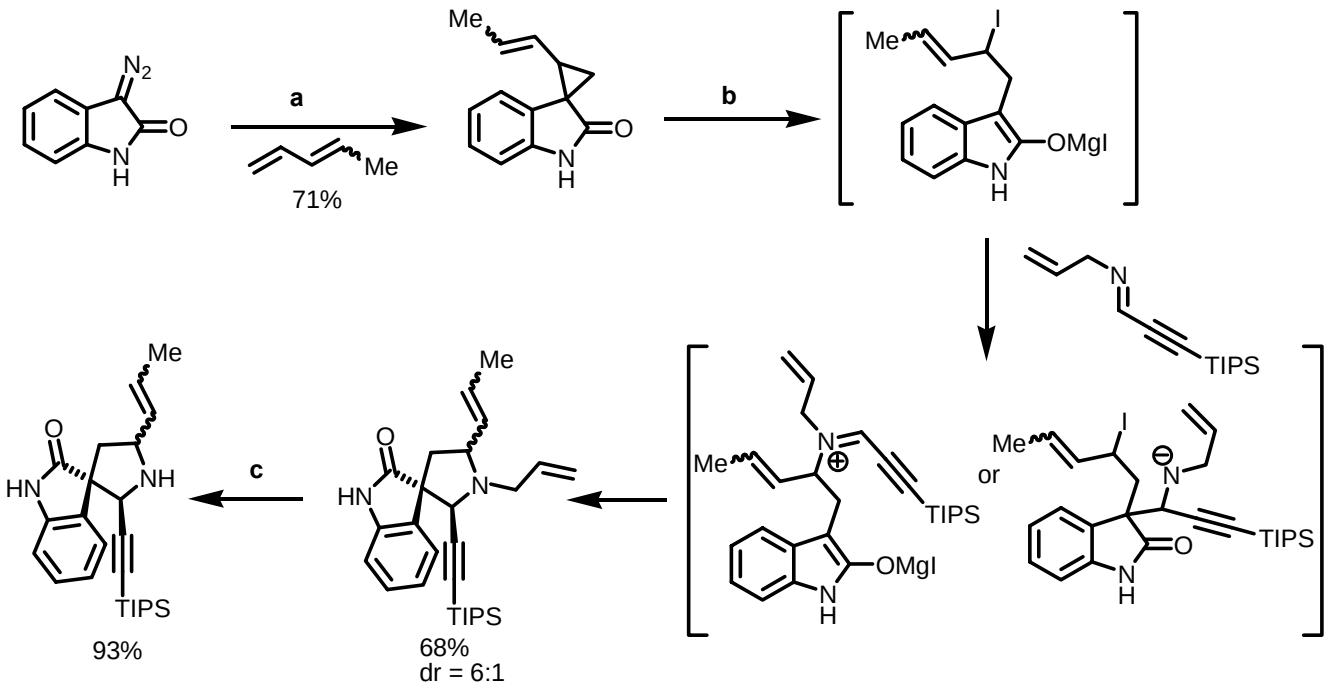


a) i. *m*-CPBA (1.1 equiv), DCM, 0 °C, 6 h; ii. PhSeSePh (0.6 equiv), $NaBH_4$ (1.2 equiv), MeOH, reflux, 10 h; iii. 30% H_2O_2 (20 equiv), THF, 0 °C, 6 h. b) *p*-TSA (10 mol %), CH_3CN, reflux, 25 min; c) i. LiHMDS, THF, 0 °C, 30 min; ii. PhSeCl, THF, 0 °C, 2h; iii. DMDO, THF, 0 °C, 4 h; iv. 4 M HCl in dioxan, 0 °C, 30 min; v. Et_3N, DCM, 4 h.

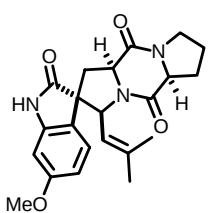




Carreira's Synthesis of Spirotryprostatin B



a) Piperylene, [{Rh(OAc)2}2] (1 mol%), benzene, reflux, slow addition of 8 in CH_2Cl_2; b) MgI_2 (1 equiv), THF, sealed tube, 75 °C;c) [$Pd(PPh_3)_4$] (6 mol%), NDMBA, CH_2Cl_2, 30 °C. TIPS=triisopropylsilyl,NDMBA=1,3-dimethylbarbituric acid.



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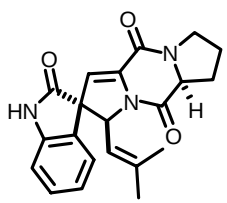
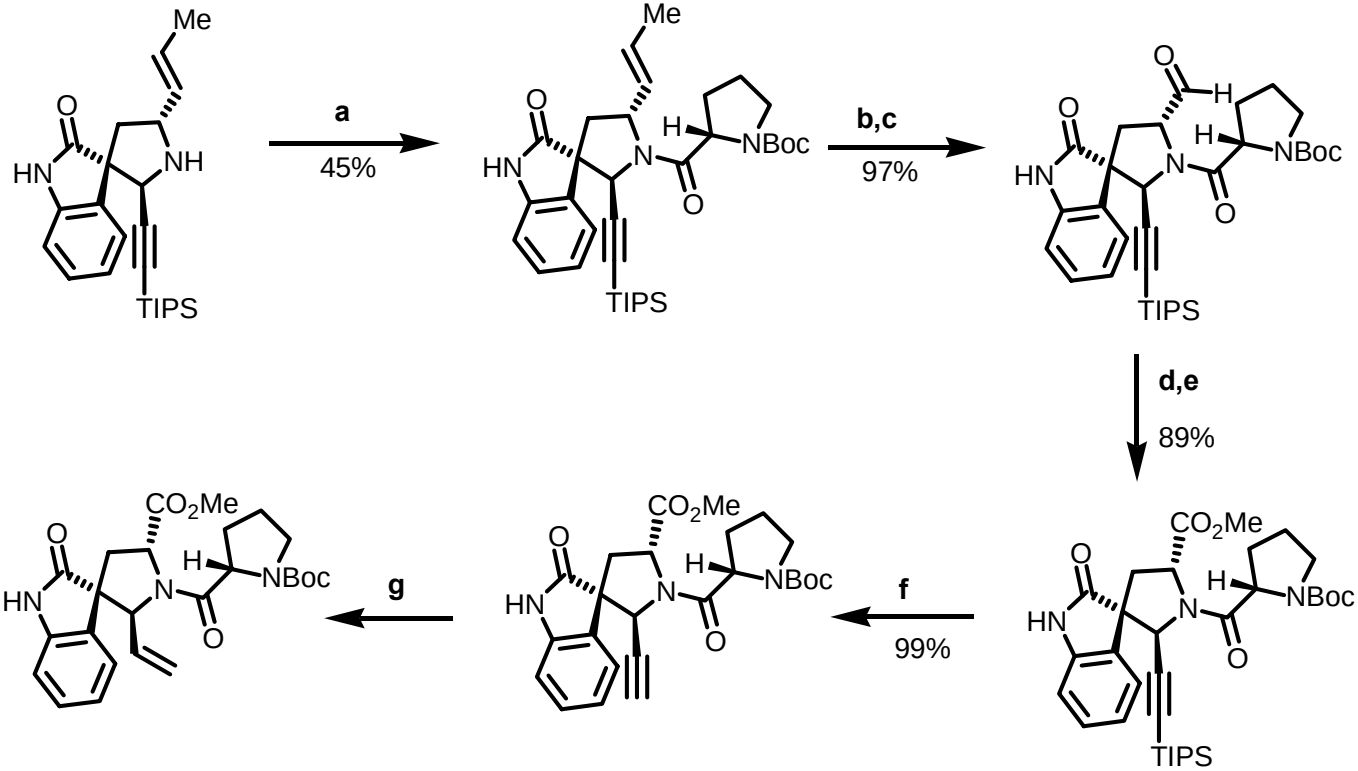
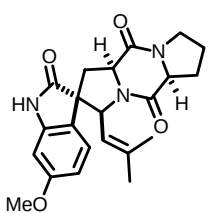
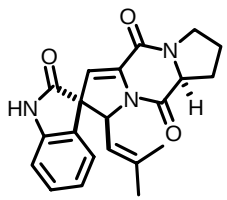


Carreira's Synthesis of Spirotryprostatin B

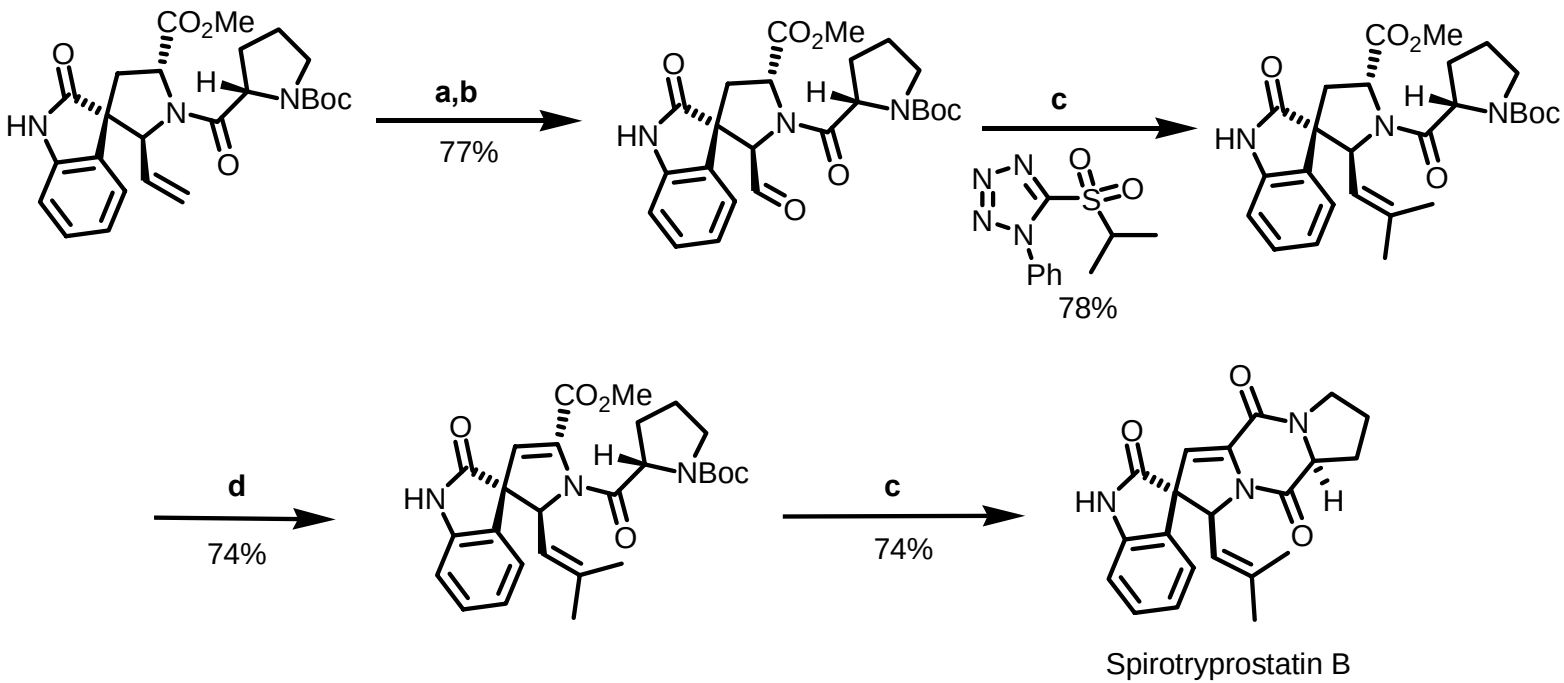


a) NEt_3, Boc-l-ProCl, CH_2Cl_2, RT; b) $NMO{\cdot}H_2O$, OsO_4 (4 mol%), THF/tBuOH/H_2O 4:4:1, RT; c) $Pb(OAc)_4$, EtOAc, rt; d) $NaClO_2$, 2-methyl-2-butene, *t*BuOH, pH 3.6 buffer, rt; e) CH_2N_2, Et_2O, RT; f) TBAF, THF, rt; g) H_2, $Pd/BaSO_4$ (33 wt%), quinoline, EtOH, RT;





Carreira's Synthesis of Spirotryprostatin B



a) $NMO{\cdot}H_2O, OsO_4$ (1 equiv), THF/*t*BuOH/H_2O 4:4:1, rt; b) $Pb(OAc)_4$, EtOAc, rt;
c) LHMDS, THF, 78 °C; d) 1. PhSeCl, LHMDS, THF,0 °C; 2. DMDO, THF, 0 °C;
e) i. TFA, CH_2Cl_2, RT; ii. NEt_3, CH_2Cl_2, rt.