Late-Stage Diversification of Natural Products

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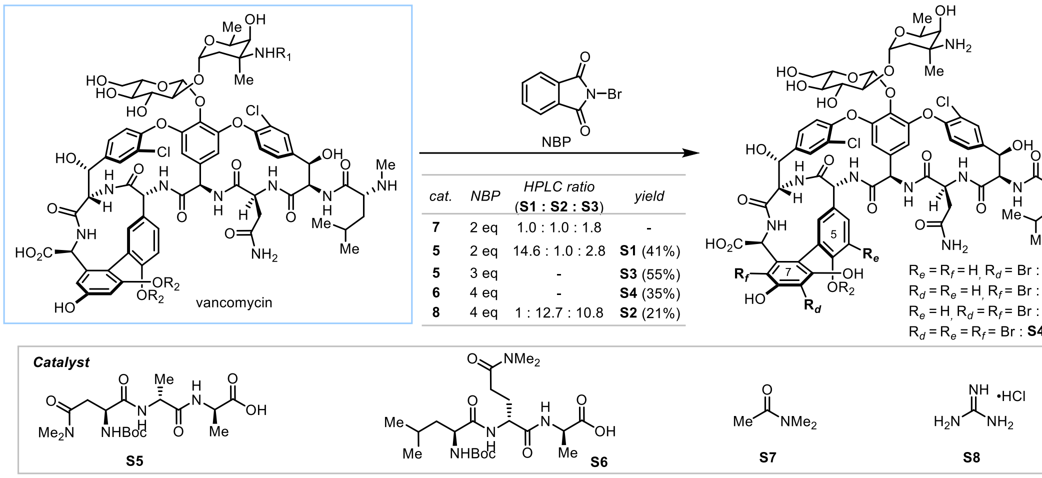
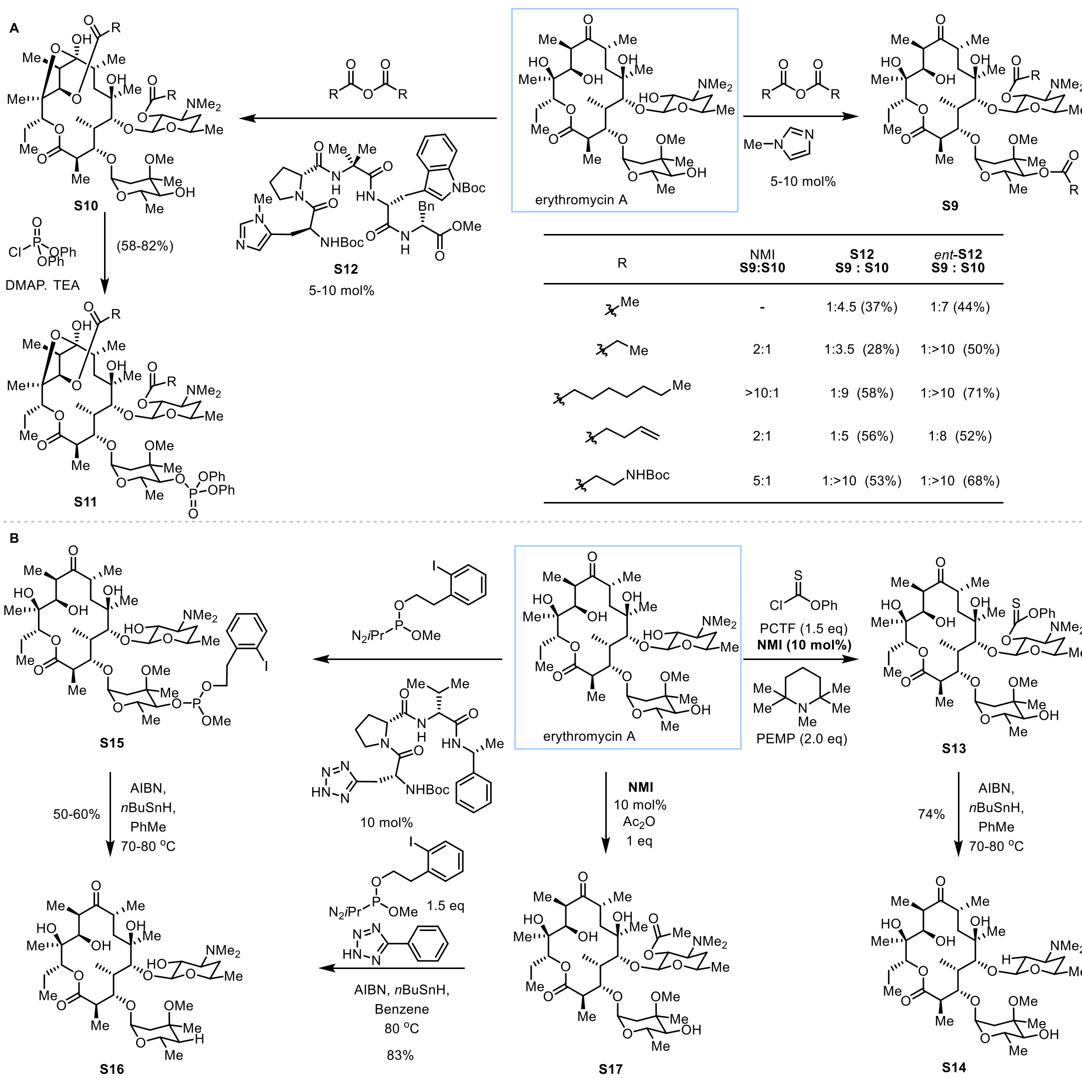
Supporting Information



cat.	*NBP*	*HPLC ratio* (**S1** : **S2** : **S3**)	*yield*
7	2 eq	1.0 : 1.0 : 1.8	-
5	2 eq	14.6 : 1.0 : 2.8	**S1** (41%)
5	3 eq	-	**S3** (55%)
6	4 eq	-	**S4** (35%)
8	4 eq	1 : 12.7 : 10.8	**S2** (21%)

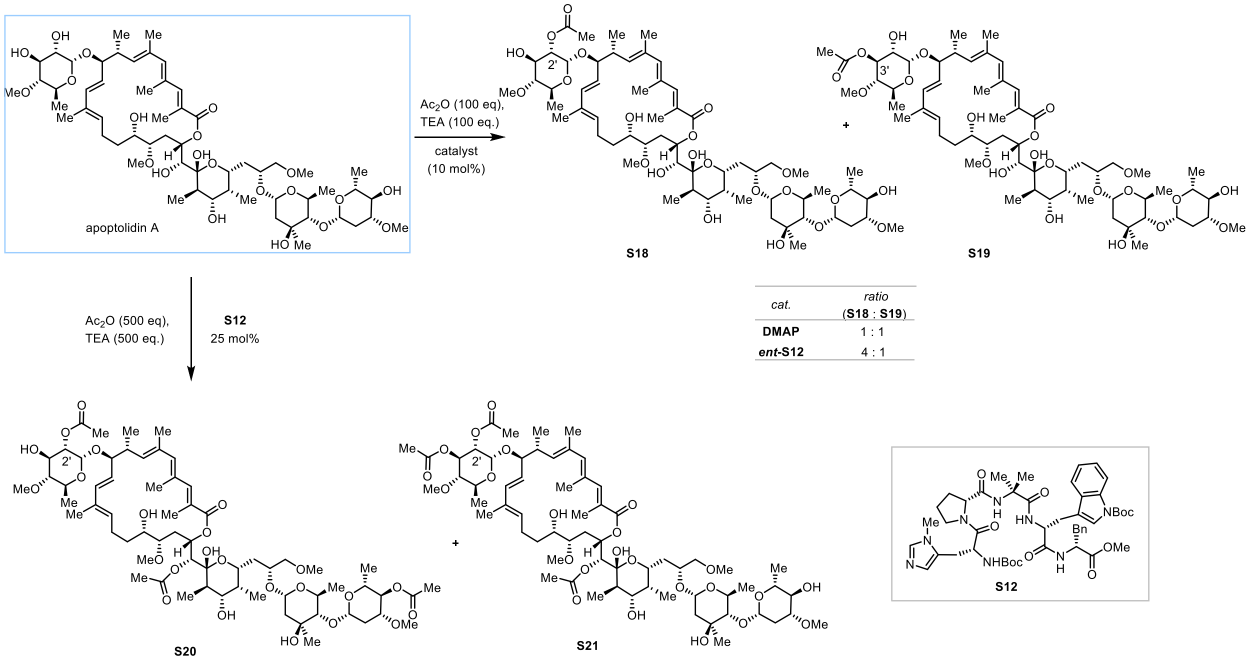
Scheme S1. Late-stage selective bromination of vancimycin.[1]



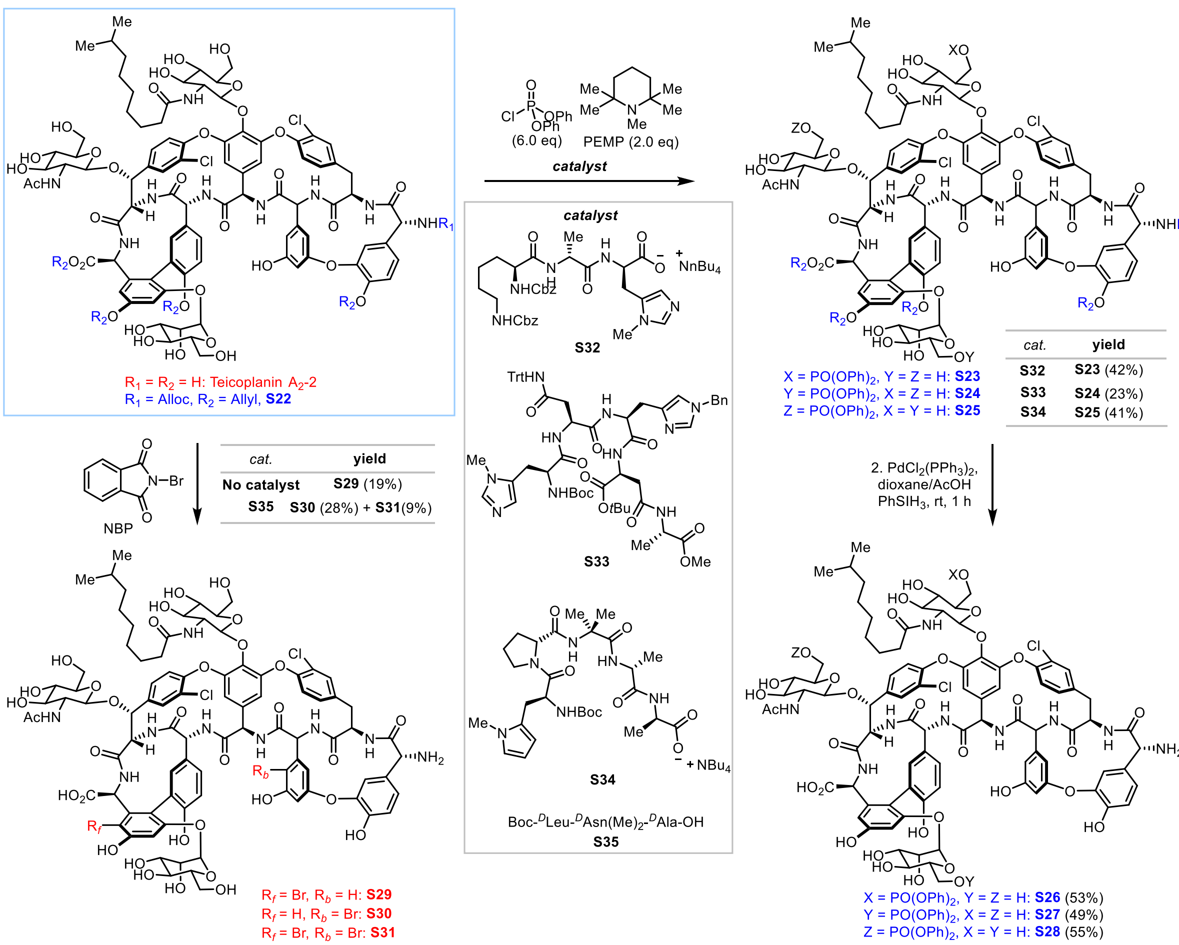
R	NMI S9:S10	S12 S9 : S10	*ent*-S12 S9 : S10
Me	-	1:4.5 (37%)	1:7 (44%)
Me	2:1	1:3.5 (28%)	1:>10 (50%)
Me	>10:1	1:9 (58%)	1:>10 (71%)
	2:1	1:5 (56%)	1:8 (52%)
NHBoc	5:1	1:>10 (53%)	1:>10 (68%)

Scheme S2. (A) Late-stage selective acylation of erythromycin A.[2,3] (B) Late-stage selective deoxygenation of erythromycin A.[4]

1. Pathak T. P.; Miller, S. J. Site-Selective Bromination of Vancomycin. *J. Am. Chem. Soc.* **2012**, *134*, 6120−6123.
2.Lewis, C. A.; Miller, S. J. Site-Selective Derivatization and Remodeling of Erythromycin A by Using Simple Peptide-Based Chiral Catalysts. *Angew. Chem., Int. Ed.* **2006**, *45*, 5616−5619.
3. Lewis, C. A.; Merkel, J.; Miller, S. J. Catalytic Site-Selective Synthesis and Evaluation of a Series of Erythromycin Analogs. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6007−6011.
4.Jordan, P. A.; Miller, S. J. An Approach to the Site-Selective Deoxygenation of Hydroxy Groups Based on Catalytic Phosphoramidite Transfer. *Angew. Chem., Int. Ed.* **2012**, *51*, 2907−2911.



Scheme S3. Late-stage selective acylation of apoptolidin A.[5]



Scheme S4. Late-stage selective acylation of teicoplanin A2-2.[6,7]

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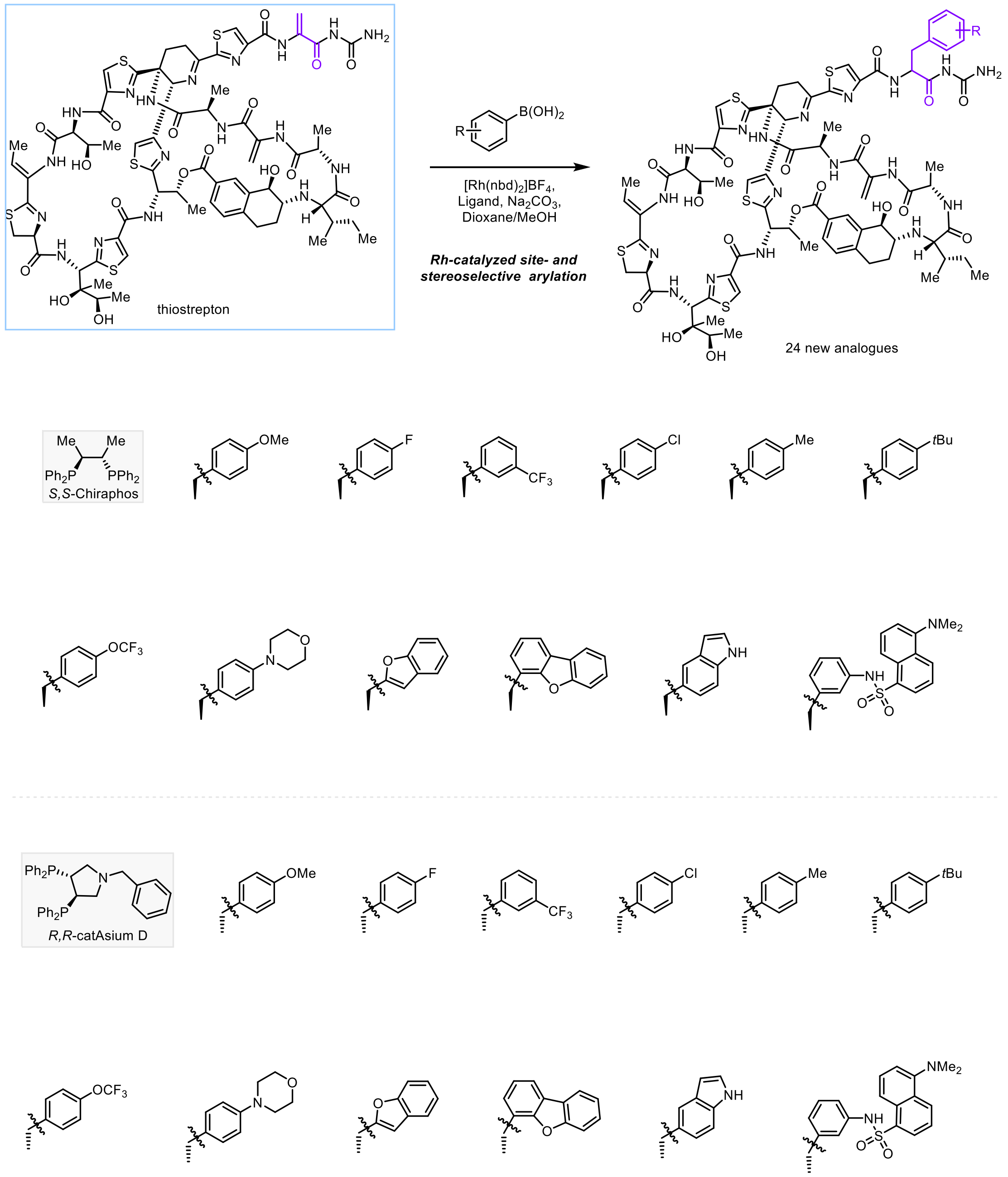
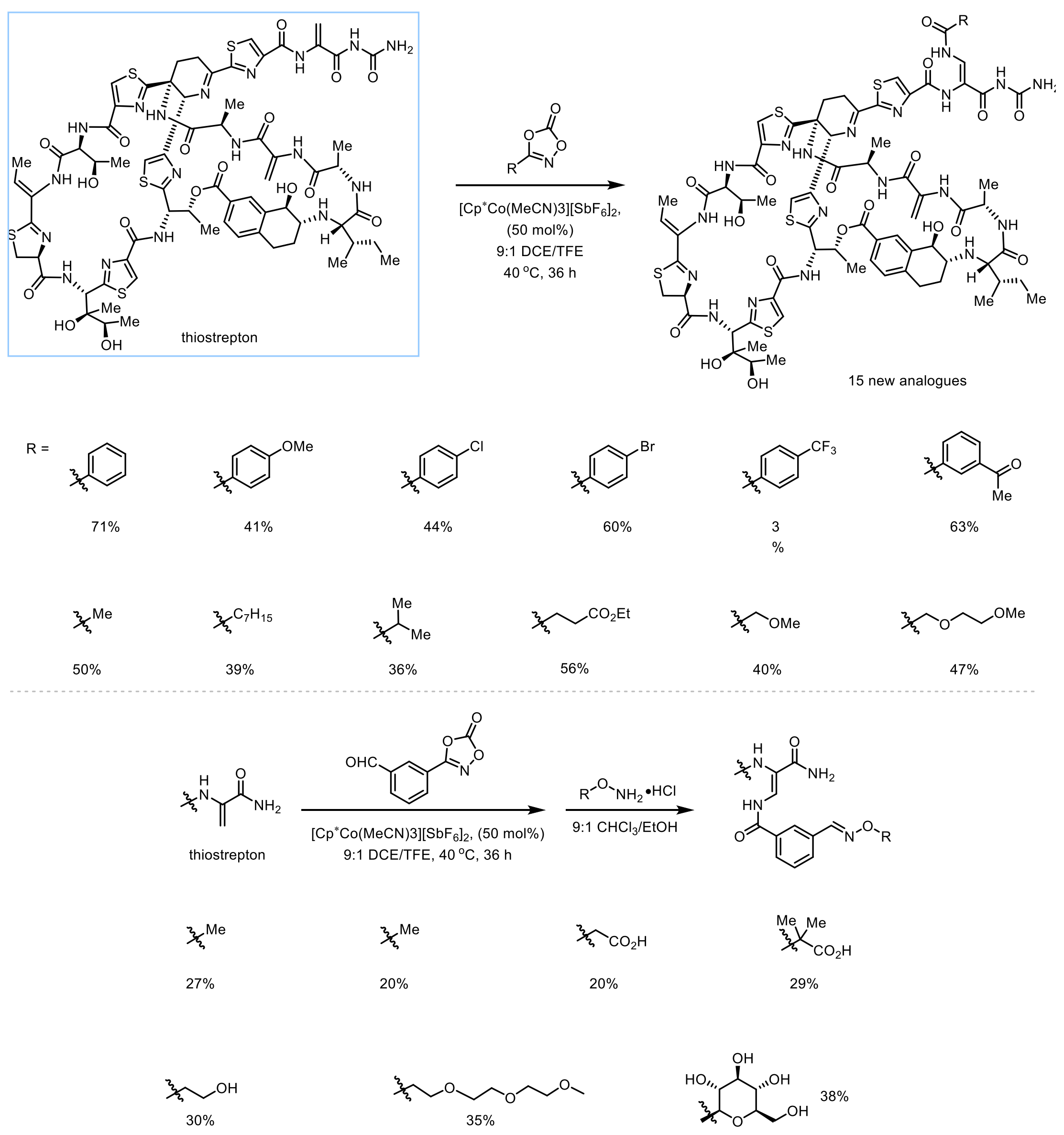
5. Lewis, C. A.; Longcore, K. E.; Miller, S. J.; Wender, P. A. An Approach to the Site-Selective Diversification of Apoptolidin A with Peptide-Based Catalysts. *J. Nat. Prod.* **2009**, *72*, 1864−1869.
6. Han, S.; Miller, S. J. Asymmetric Catalysis at a Distance: Catalytic, Site-Selective Phosphorylation of Teicoplanin. *J. Am. Chem. Soc.* **2013**, *135*, 12414−12421.
7. Pathak, T. P.; Miller, S. J. Chemical Tailoring of Teicoplanin with Site-Selective Reactions. *J. Am. Chem. Soc.* **2013**, *135*, 8415−8422.



Scheme S5. Late-stage diversification of thiostrepton via Rh-catalyzed site- and stereoselective arylation.[8]

8. Key, H. M.; Miller, S. J. Site- and Stereoselective Chemical Editing of Thiostrepton by Rh-Catalyzed Conjugate Arylation: New Analogues and Collateral Enantioselective Synthesis of Amino Acids. *J. Am. Chem. Soc.* **2017**, *139*, 15460-15466.



Scheme S6. Late-stage diversification of thiostrepton via siteselective C–H Amidation.[9]

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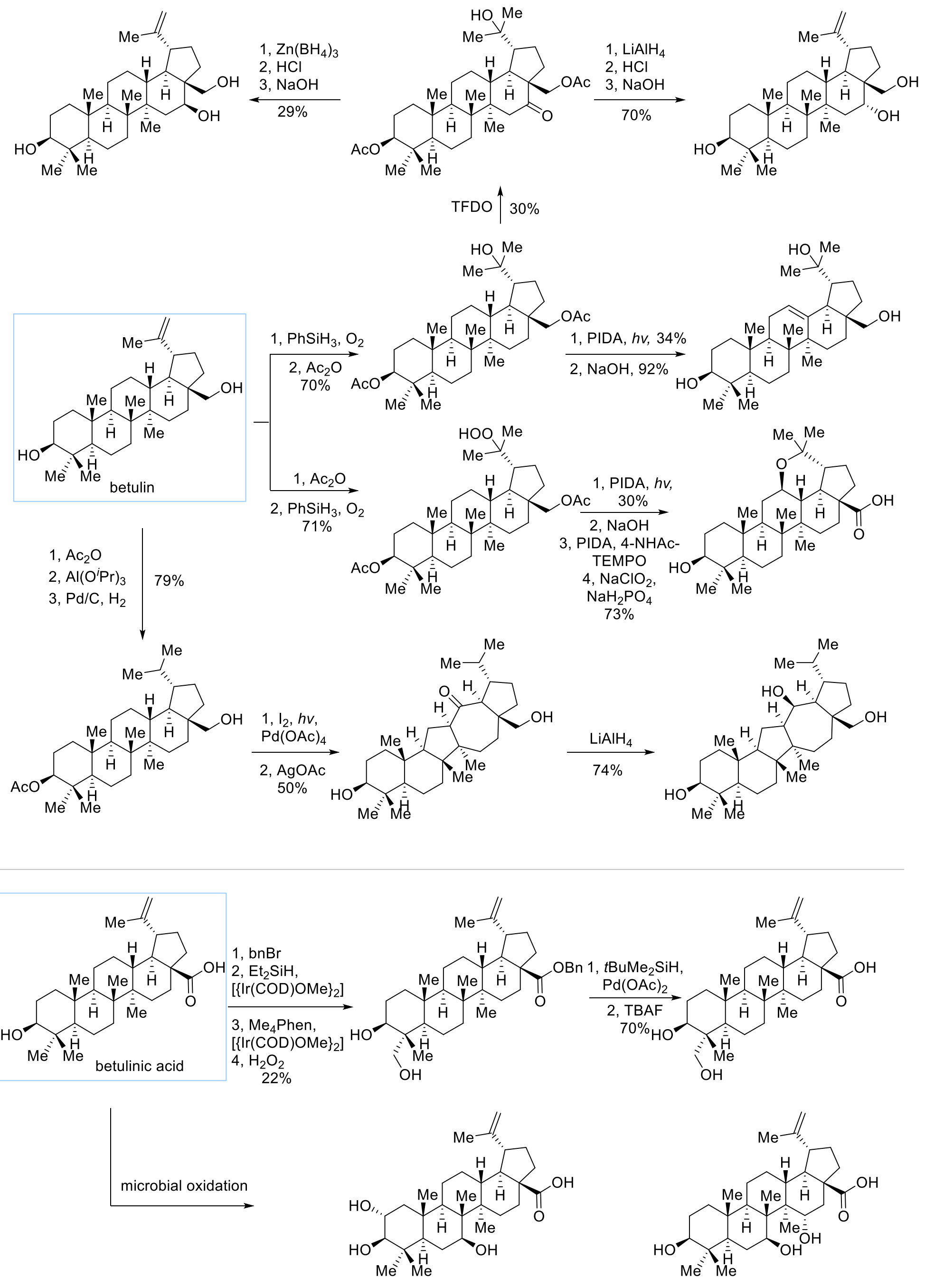
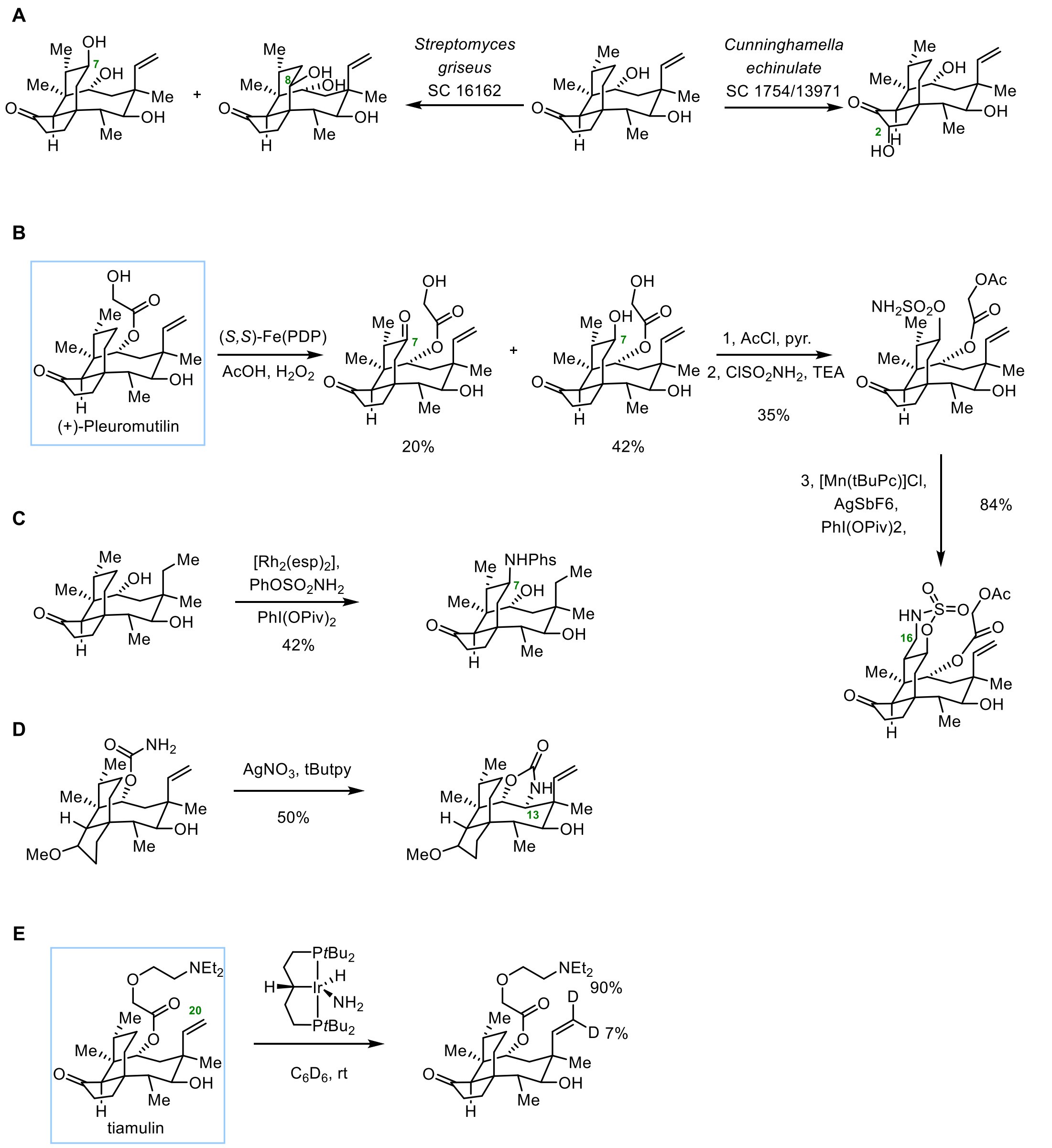
9. Scamp, R. J.; deRamon, E.; Paulson, E. K.; Miller, S. J.; Ellman. J. A. Co (III)-Catalyzed C–H Amidation of Dehydroalanine for the Site-Selective Structural Diversification of Thiostrepton. *Angew. Chem. Int. Ed.* **2020**, *59*, 890-895.



Scheme S7. Late-stage diversification of betulin and betulinic acid via C–H oxidation.[10]

10. Michaudel, Q.; Journot, G.; Regueiro-Ren, A.; Goswami, A.; Guo, Z.; Tully, T. P.; Zou, L.; Ramabhadran, R. O.; Houk, K. N.; Baran, P. S. Improving Physical Properties via C-H Oxidation: Chemical and Enzymatic Approaches. *Angew. Chem. Int. Ed.* **2014**, *53*, 12091 -12096.



Scheme S8. Late-stage diversification of pleuromutilin skeleton. (A) Microbial oxidation.[11] (B) C7 oxidation[12] and C16 amination[13]. (C) C7 amination.[14] (D) C13 amination.[15] (E) C20 deuteration.[16]

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11. Hanson, R. L.; Matson, J. A.; Brzozowski, D. B.; LaPorte, T. L.; Springer, D. M.; Patel, R. N. Hydroxylation of Mutilin by Streptomyces griseus and Cunninghamella echinulata. *Org. Pro. Res. Dev.* **2002**, *6*, 482-487.
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14. Chiappini, N. D.; Mack, J. B. C.; Bois, J. D. Intermolecular sp^3 C–H Amination of Complex Molecules. *Angew. Chem. Int. Ed.* **2018**, *57*, 4956-4959.
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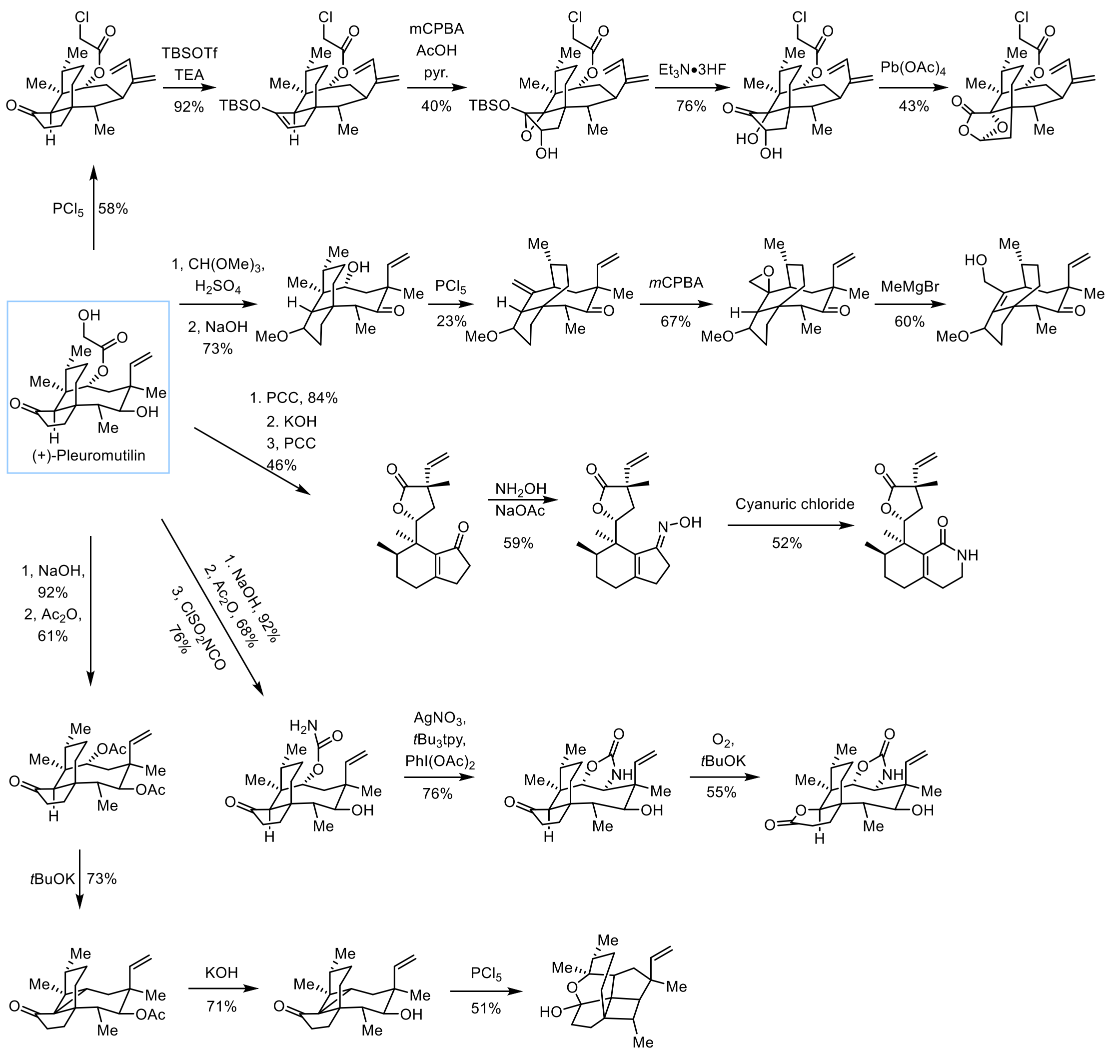
16. Zhou, J.; Hartwig, J. F. Iridium-Catalyzed H/D Exchange at Vinyl Groups without Olefin Isomerization. *Angew. Chem. Int. Ed.* **2008**, *47*, 5783–5787.



Scheme S9. Late-stage diversification of pleuromutilin skeleton via ring system distortion.[17]

17. Diverse compounds from pleuromutilin lead to a thioredoxin inhibitor and inducer of ferroptosis, Evijola Llabani, Robert W. Hicklin, Hyang Yeon Lee, Stephen E. Motika1, Lisa A. Crawford, Eranthie Weerapana and Paul J. Hergenrother, *Nat. Chem.* **2019**, *11*, 521-532.