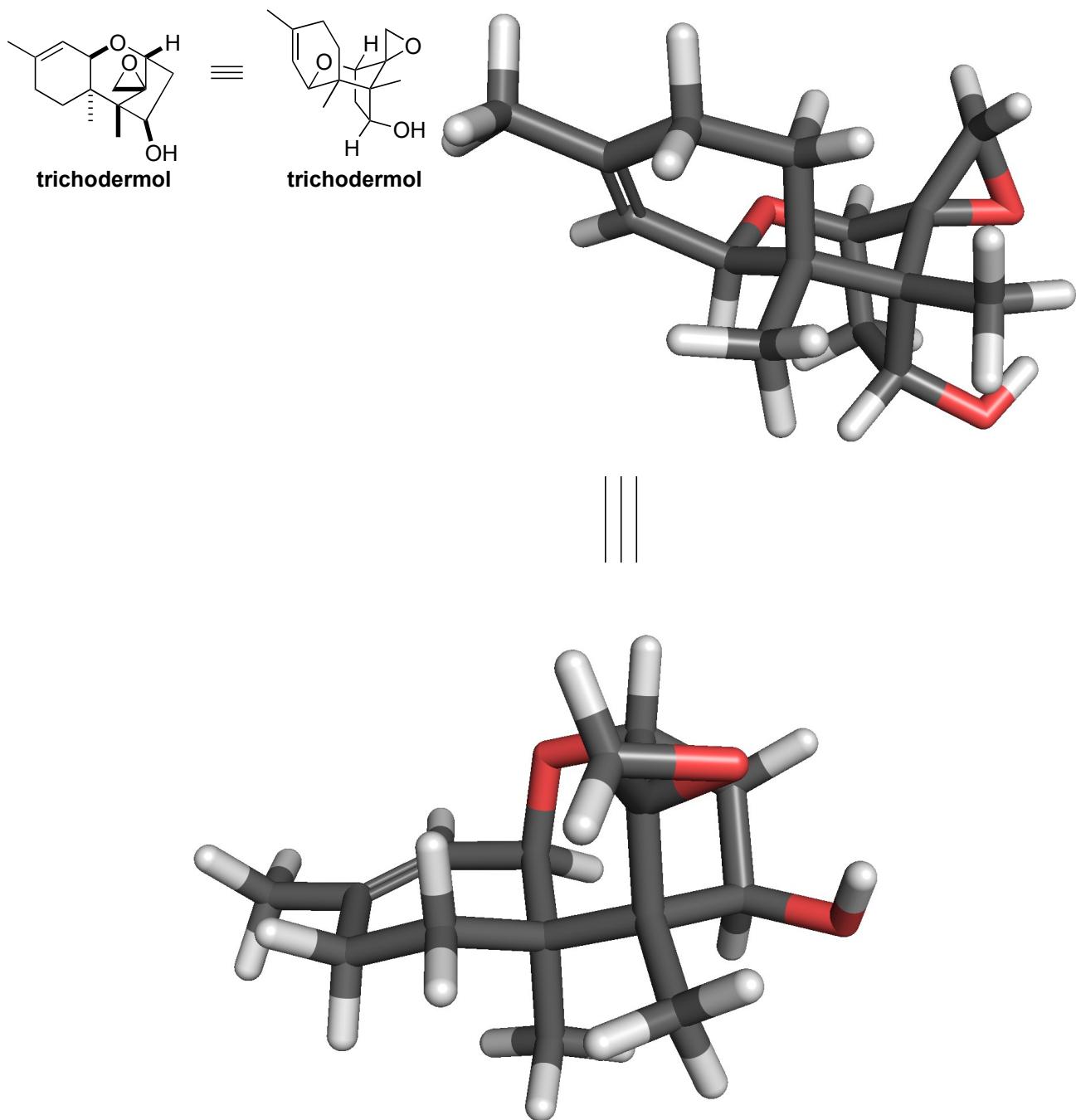


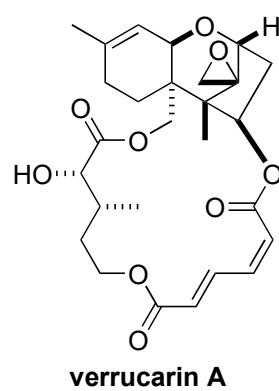
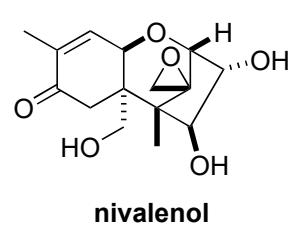
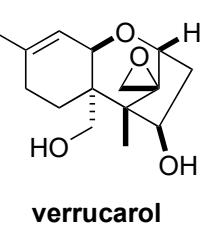
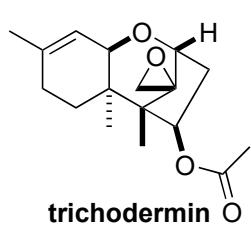
Problem Session (14)

2022/10/08 MASANORI NAGATOMO

Please propose your synthetic route to trichodermol from a commercial compound.



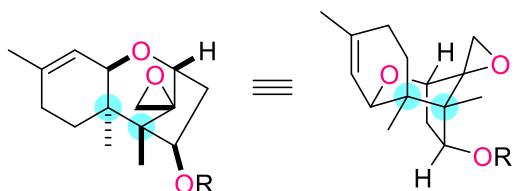
related natural products



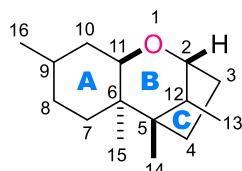
Problem Session (14)- Answer

2022/10/08 MASANORI NAGATOMO

Synthetic Plan of trichodermol



R = H: trichodermol
R = Ac: trichodermin



trichothecane skeleton

·**Isolation:** Acetylated compound trichodermine was isolated from *Trichoderma viride*.

W. O. Godtfredsen, S. Vangedal, *Proc. Chem. Soc.* **1964**, 188; *idem, Acta Chem. Scand.*, **1965**, 19, 1088.

·**Bioactivities:** Trichothecane sesquiterpenes exhibit specific biological activities, especially antifungal, antiviral, cytotoxic, and anticancer effects.

·**Structural features:** 2-Oxatricyclo[7.2.1.0^{3,8}]dodec-4-ene core structure (ABC-rings). Cis-fused AB ring.

Oxabicyclo[3.2.1] structure (BC ring). Two contiguous quaternary carbons (C5, C6). C12-exoepoxide.

Total synthesis

trichodermin: Colvin, E. W.; Raphael, R. A.; Roberts, J. S. *J. Chem. Soc. D: Chem. Commun.* **1971**, 858 (racemic).

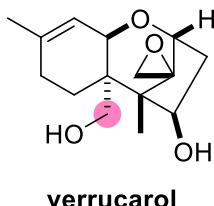
trichodermol: a) Still, W. C.; Tsai, M.-Y. *J. Am. Chem. Soc.* **1980**, 102, 3654 (racemic). b) O'Brien, M. K.; Pearson, A. J.; Pinkerton, A. A.; Schmidt, W.; Willman, K. *J. Am. Chem. Soc.* **1989**, 111, 1499 (racemic).

calonectrin: a) Kraus, G. A.; Roth, B.; Frazier, K.; Shimagaki, M. *J. Am. Chem. Soc.* **1982**, 104, 1114 (racemic). b) Tomioka, K.; Sugimori, M.; Koga, K. *Chem. Pharm. Bull.* **1987**, 35, 906 (racemic). **anguidine:** Brooks, D. W.; Grothaus, P. G.; Mazdiyasni, H. *J. Am. Chem. Soc.* **1983**, 105, 4472. **verrucarol:** a) Schlessinger, R. H.; Nugent, R. A. *J. Am. Chem. Soc.* **1982**, 104, 1116 (racemic). b) Trost, B. M.; McDougal, P. G. *J. Am. Chem. Soc.* **1982**, 104, 6110 (racemic). c) Roush, W. R.; D'Ambra, T. E. *J. Am. Chem. Soc.* **1983**, 105, 1058 (racemic). d) Koreeda, M.; Ricca, D. J.; Luengo, J. I. *J. Org. Chem.* **1988**, 53, 5586 (racemic, formal). d) Ishihara, J.; Nonaka, R.; Terasawa, R.; Shiraki, K.; Yabu, H.; Kadota, Y.; Ochiai, K.; Tadano, K. *J. Org. Chem.* **1998**, 63, 2679.

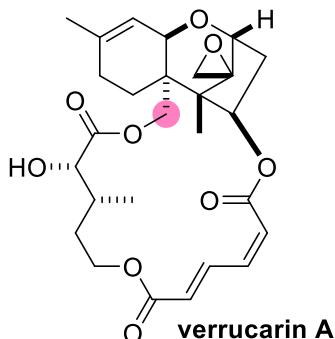
Reviews

a) Tori, M. *J. Synth. Org. Chem. Jpn.* **1981**, 39, 642. b) Heathcock, C. H.; Graham, S. L.; Pirrung, M. C.; Plavac, F.; White, C. T. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; John Wiley and Sons: New York, 1983; Vol. 5, pp 238. c) McDougal, P. G.; Schmuff, N. R. *Prog. Chem. Org. Nat. Prod.* **1985**, 47, 153.

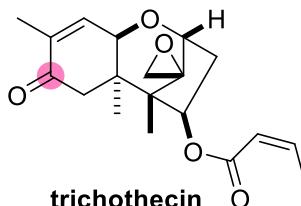
related natural products



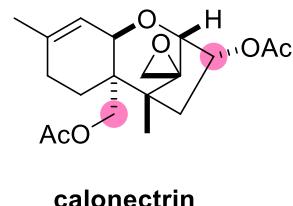
verrucarol



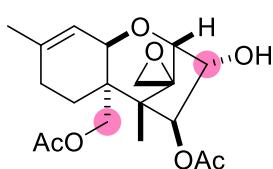
verrucarin A



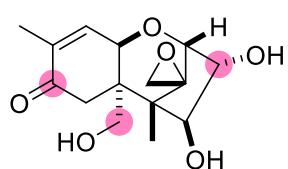
trichothecin



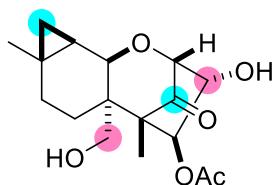
calonectrin



anguidine

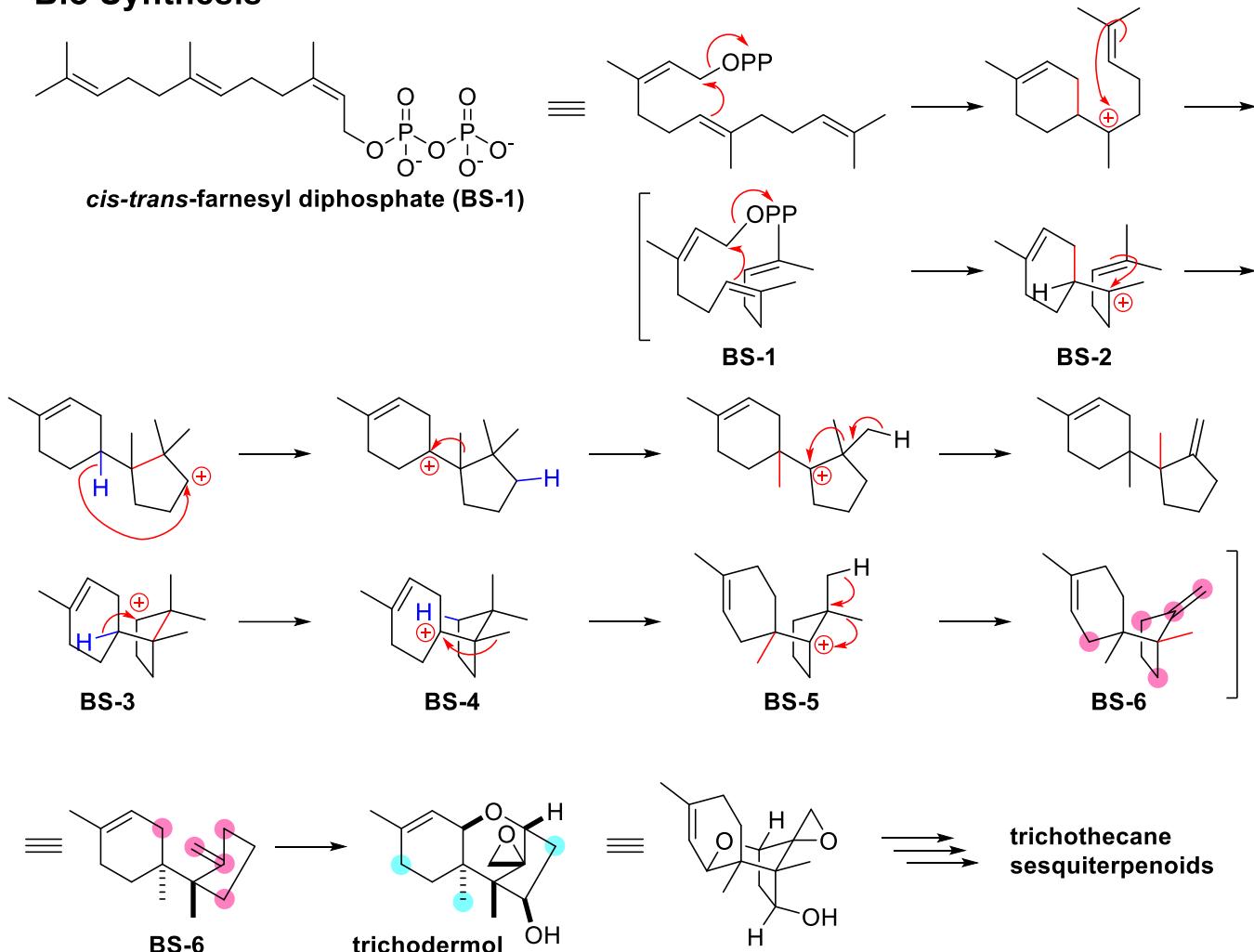


nivalenol

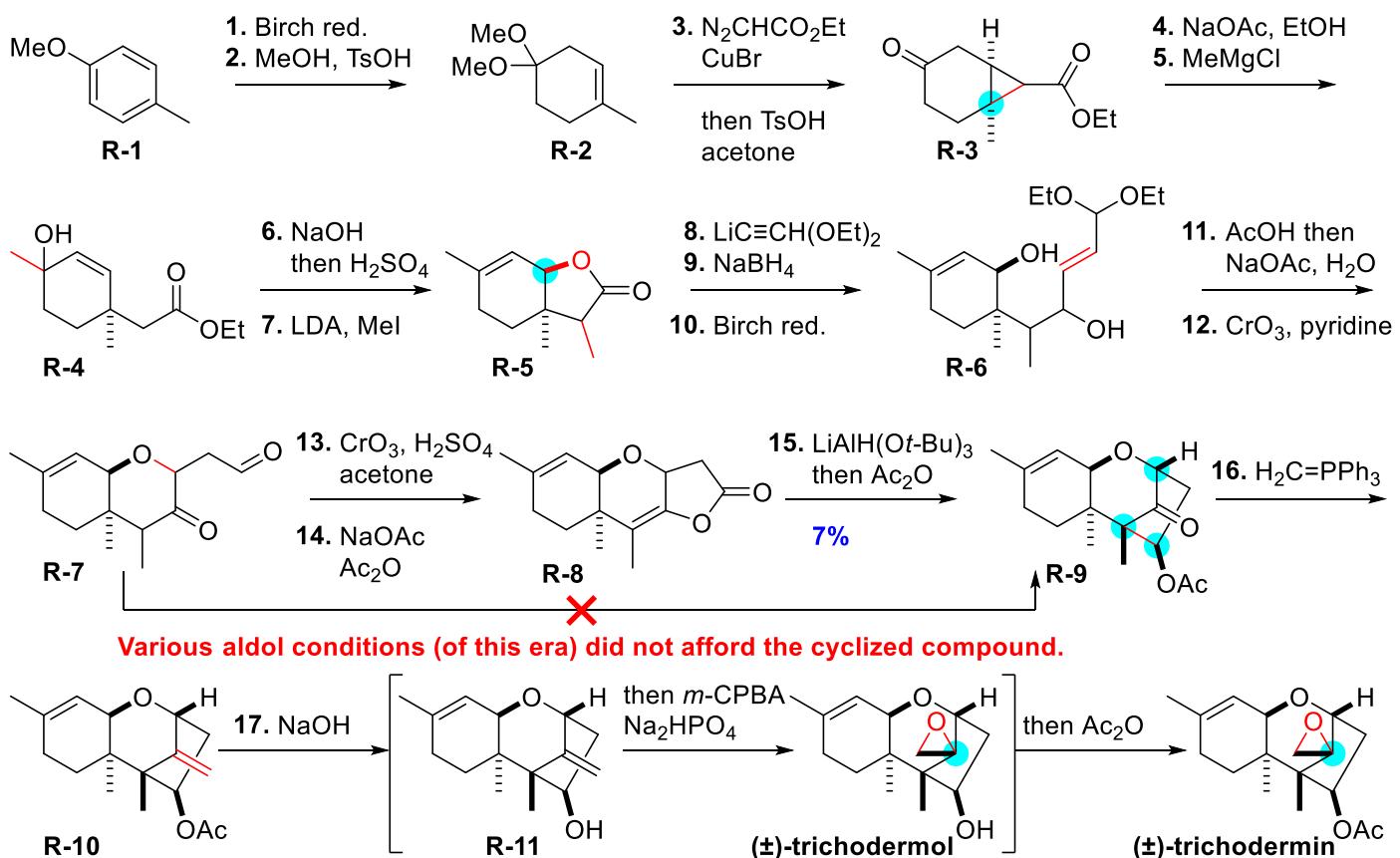


tenuipesine A

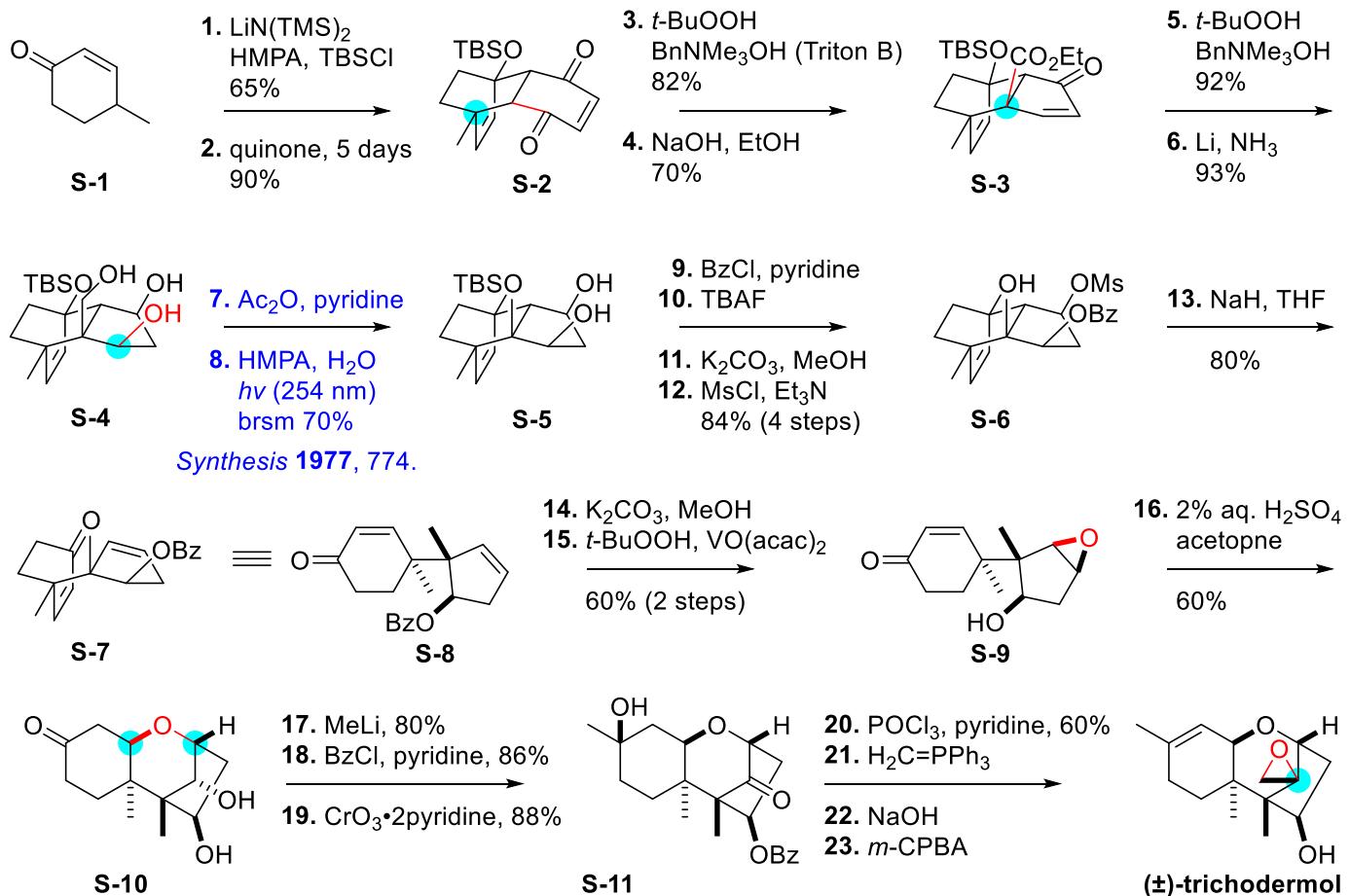
Bio Synthesis



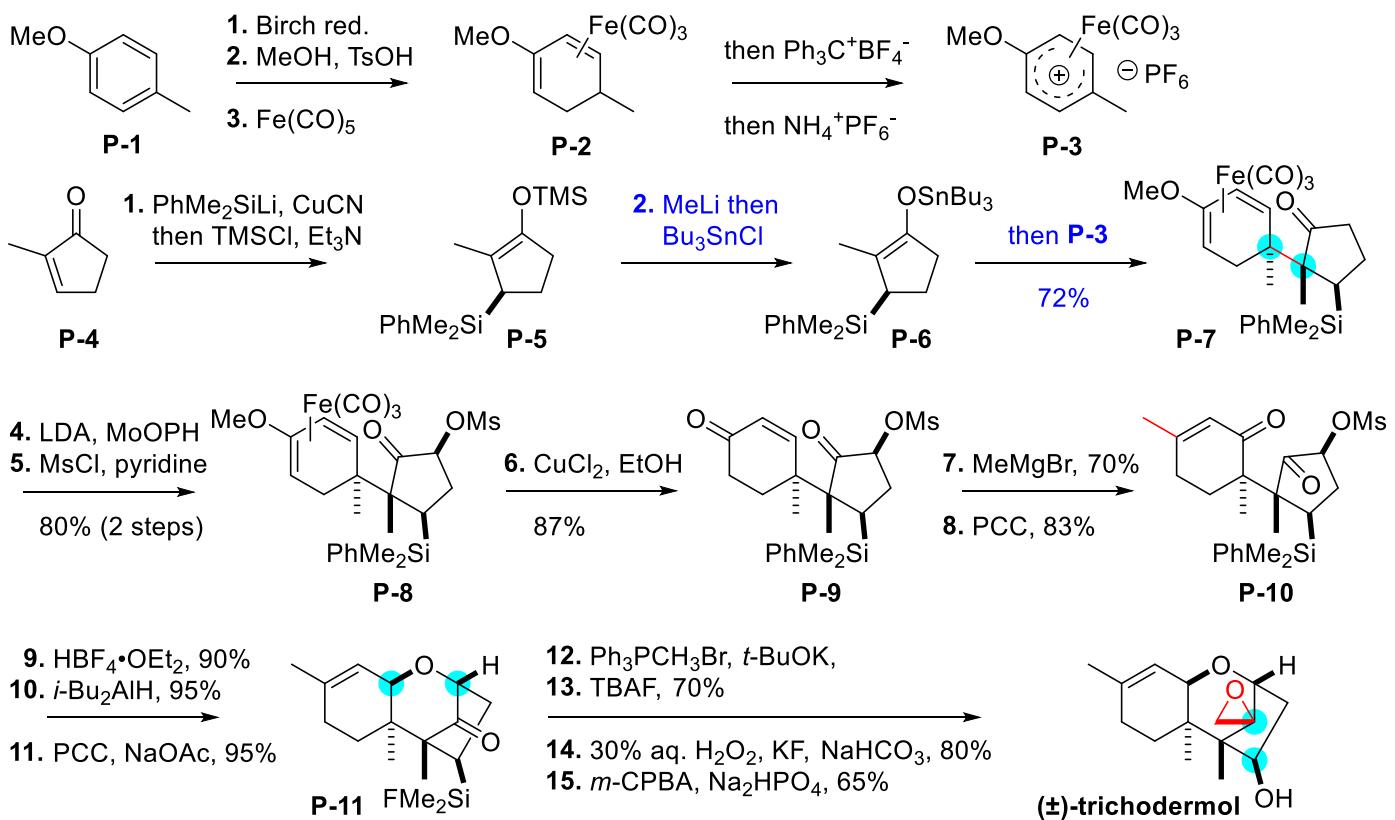
The first total synthesis of (\pm) -trichodermin by Raphael and Roberts (1971)



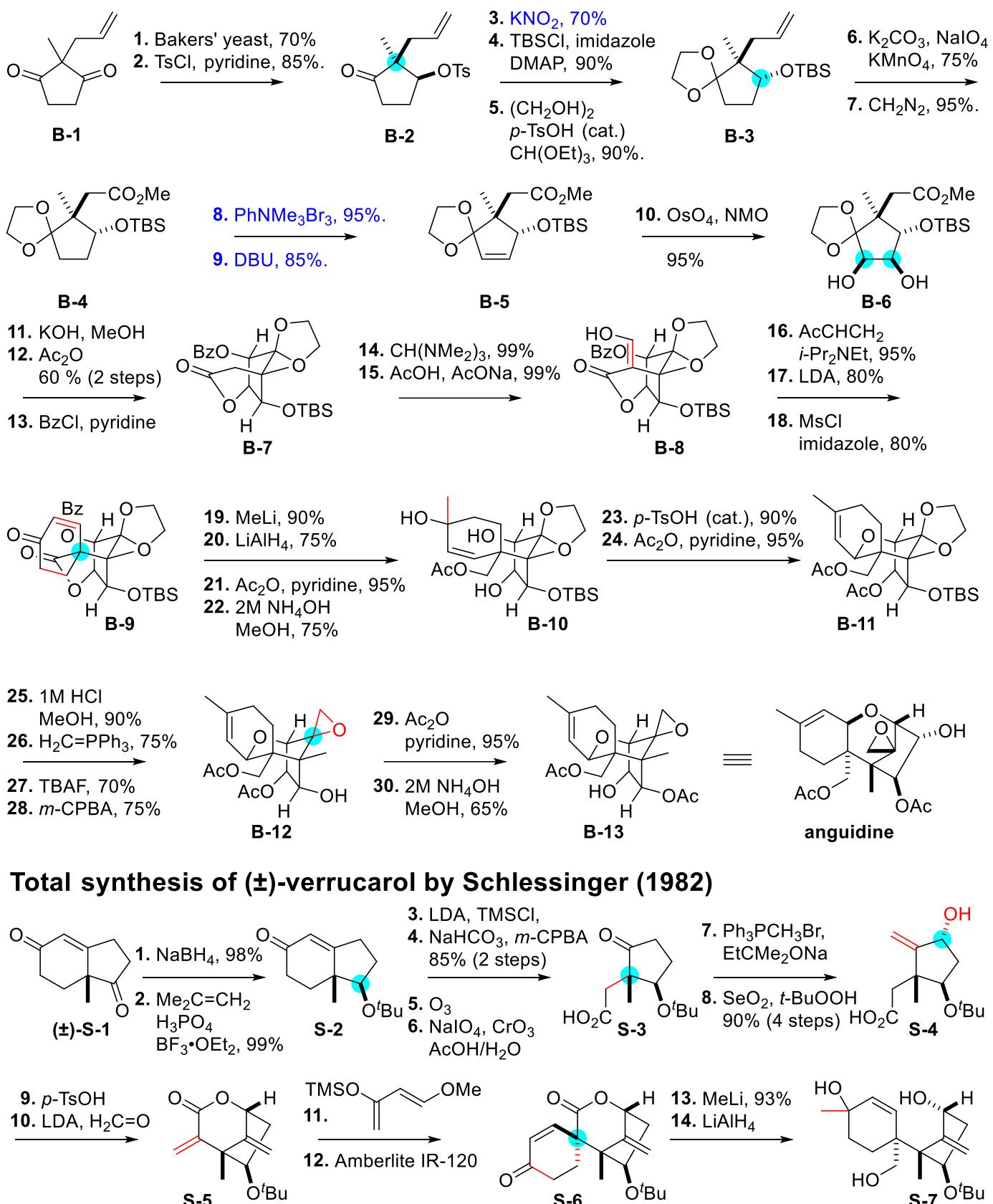
Total synthesis of (\pm)-trichodermol by Still (1980)



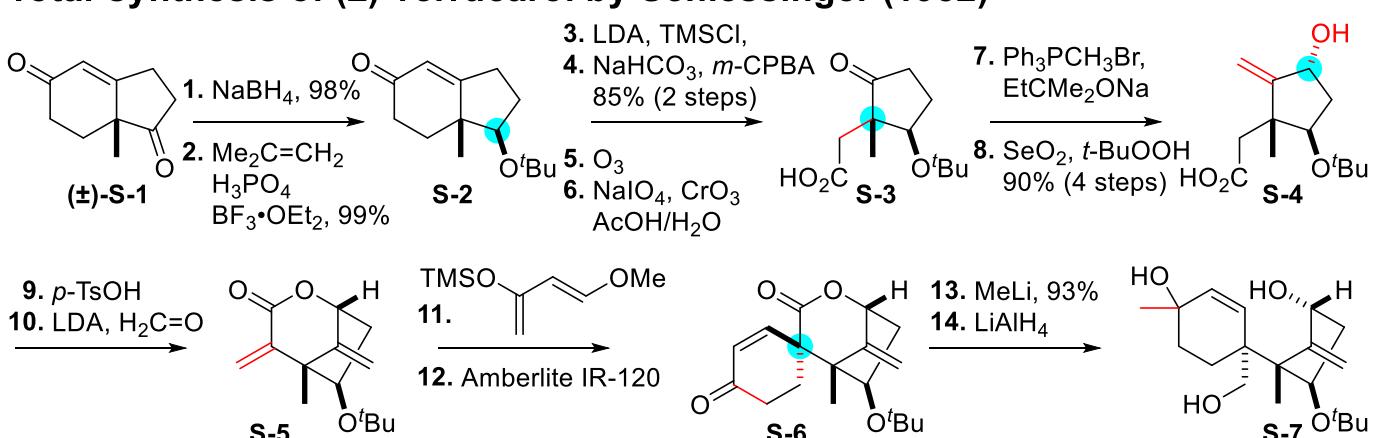
Total synthesis of (\pm)-trichodermol by Pearson (1989)



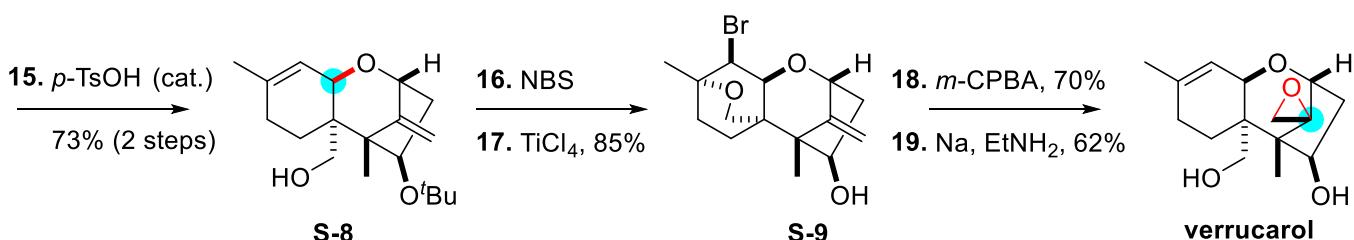
Asymmetric total synthesis of anguidine by Brooks (1983)



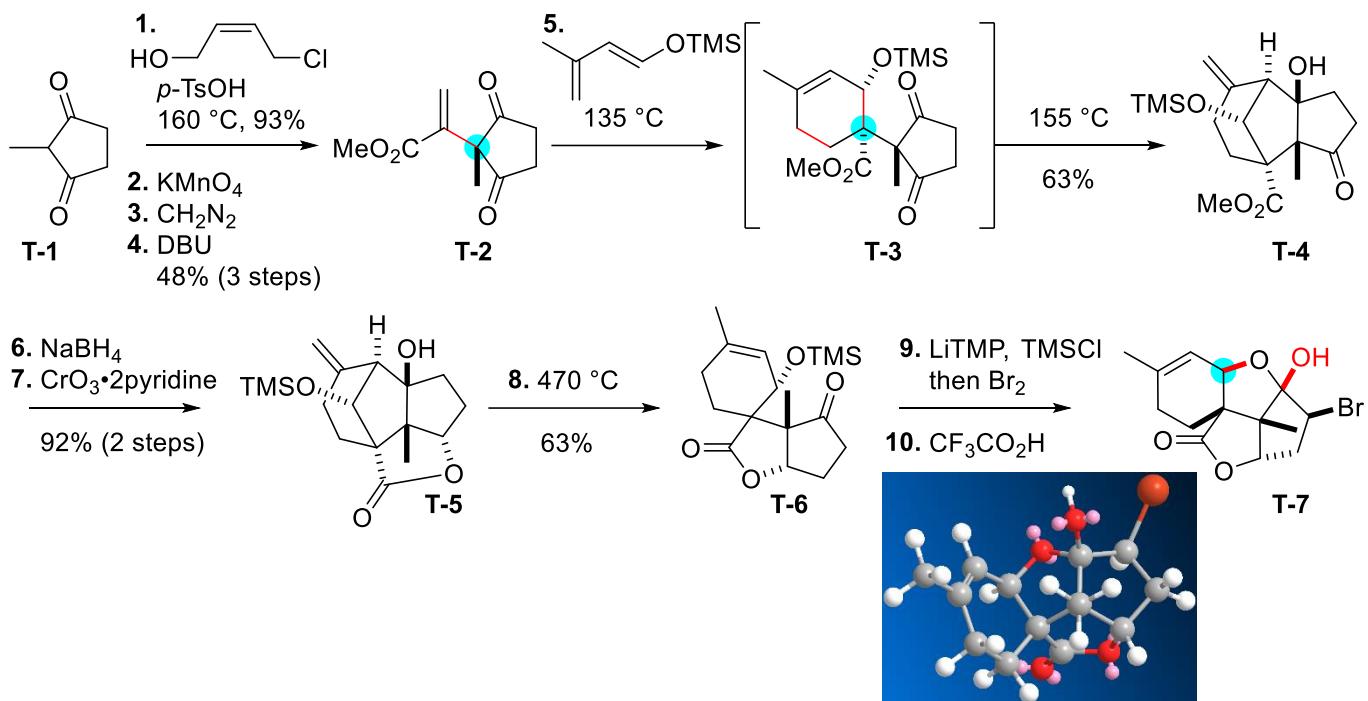
Total synthesis of (\pm)-verrucarol by Schlessinger (1982)



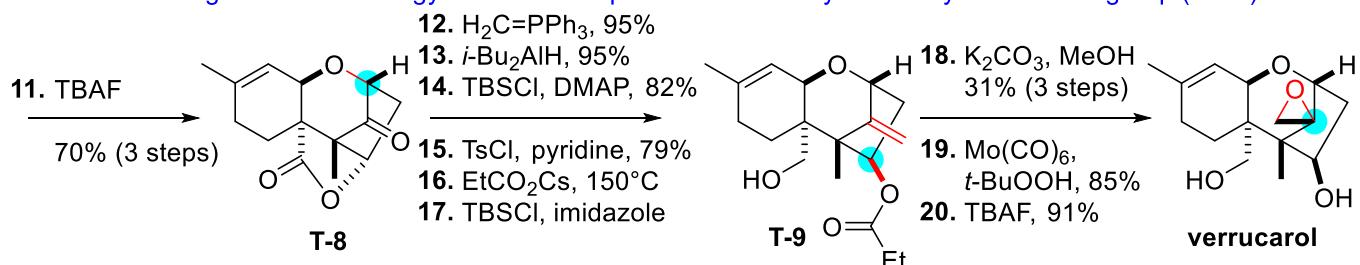
A similar DA strategy has been adopted for the total synthesis by the Roush group (1983).



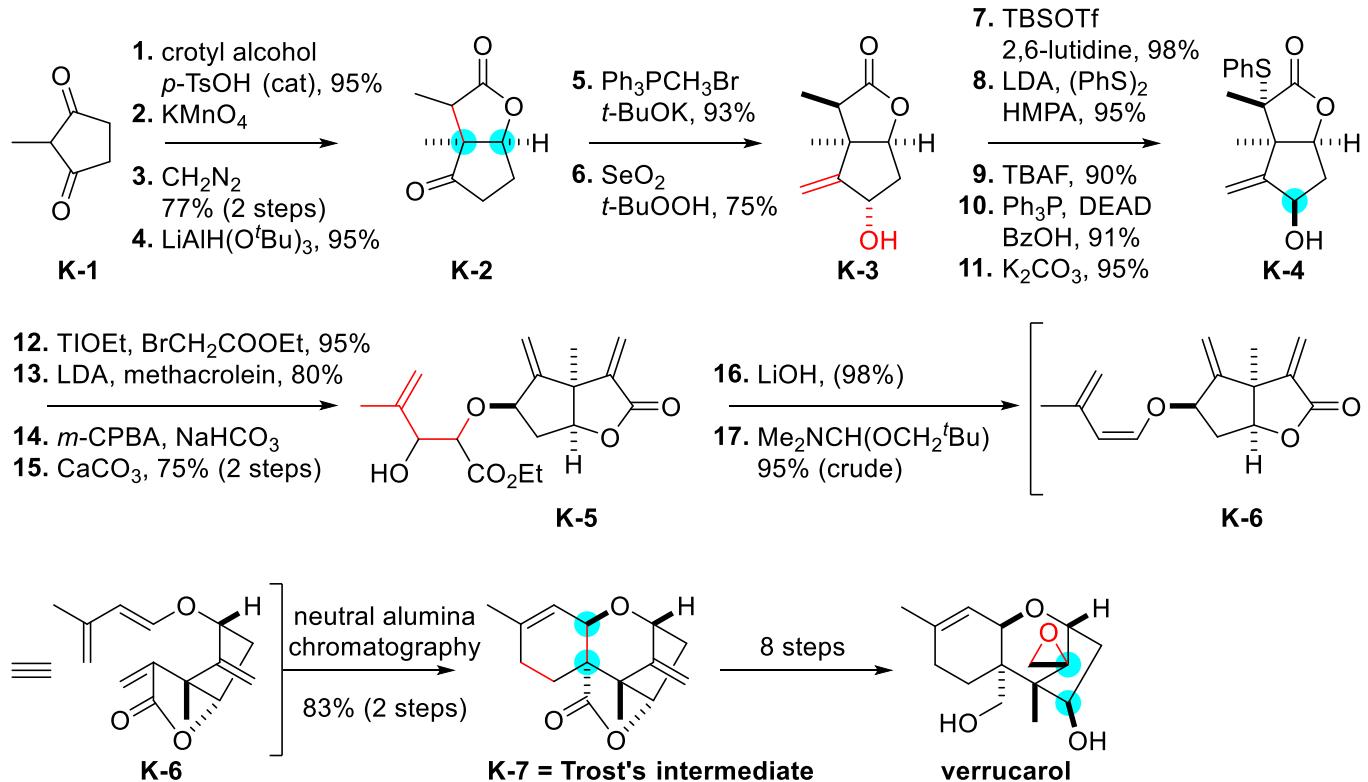
Total synthesis of (\pm)-verrucarol by Trost (1982)



A similar rearrangement??? strategy has been adopted for the total synthesis by the Tadano group (1998).



Formal total synthesis of (\pm)-verrucarol by Koreeda (1988)



Our original synthetic plans are closed to the public.