

Literature Report

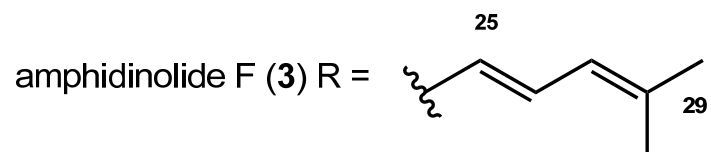
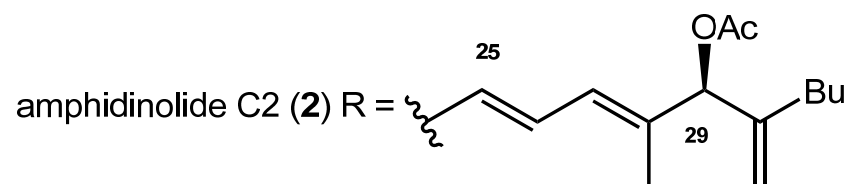
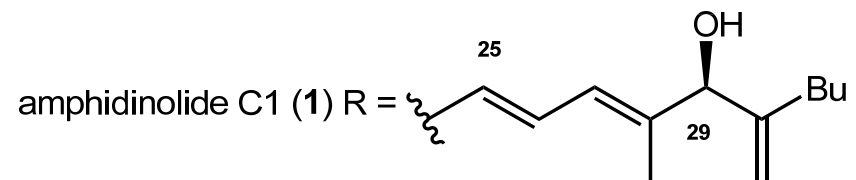
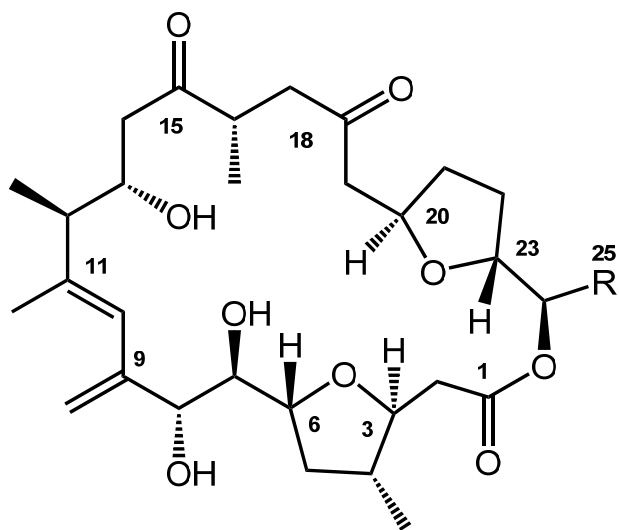
Enantioselective Total Synthesis of Amphidinolide F

Reporter: Mu-Wang Chen
Checker: Ran-Ning Guo

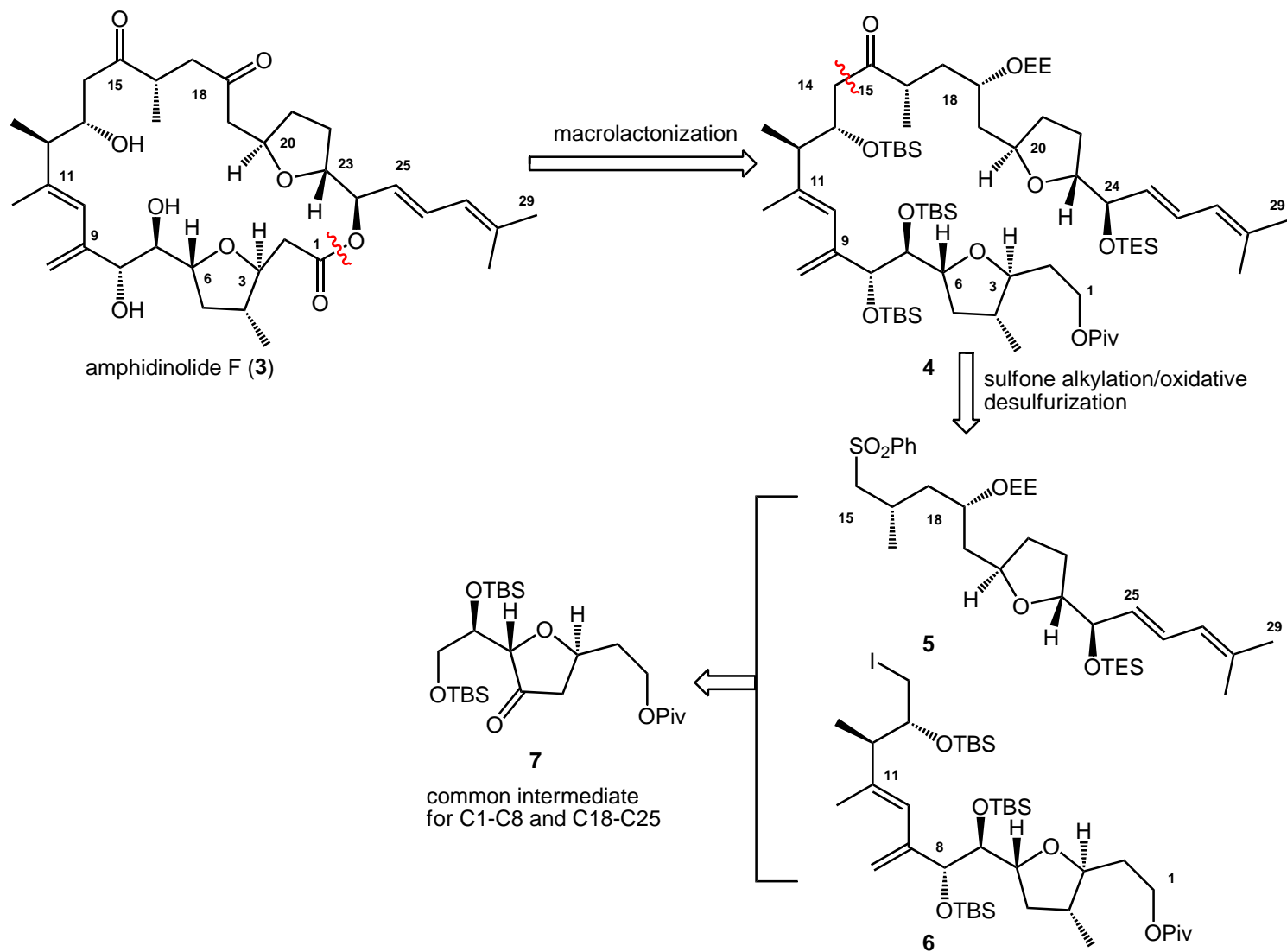
Carter, R. G. *et al.*
Angew.Chem. Int. Ed. 2012, 51, 7948-7951



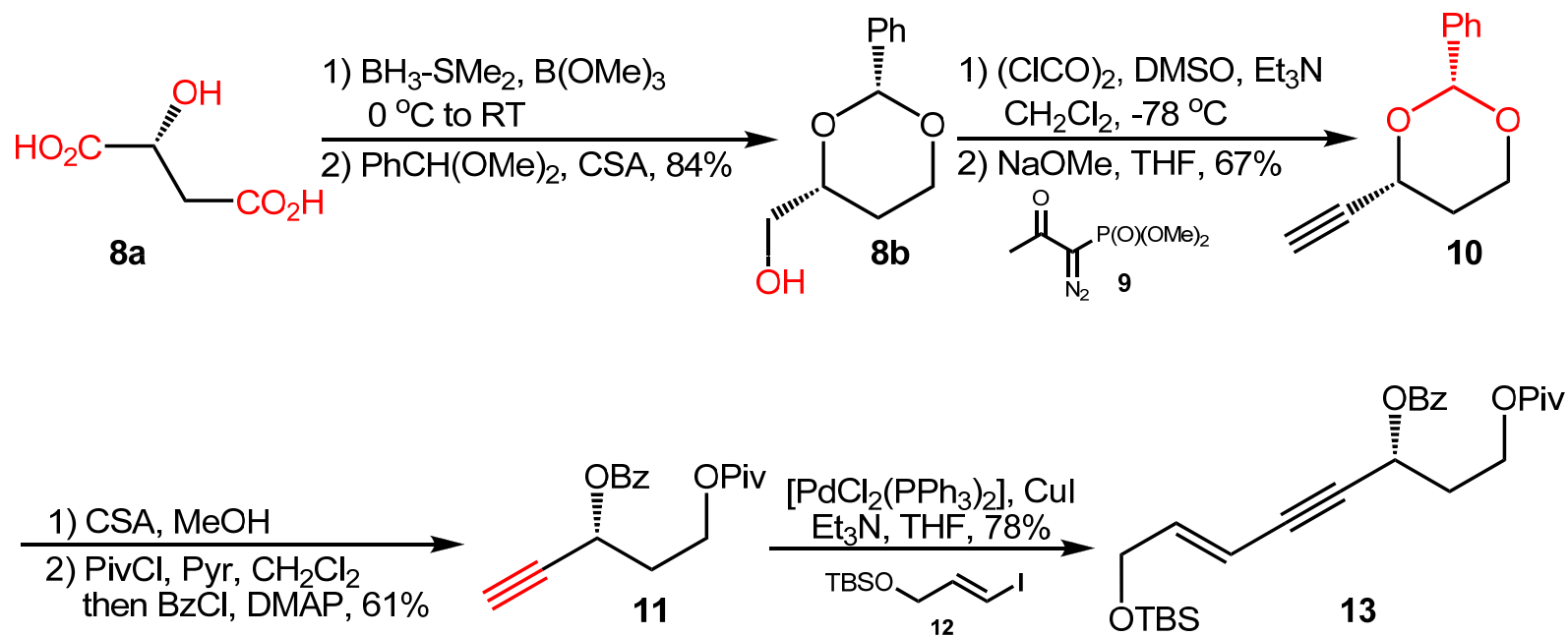
Structurally complex amphidinolide natural products

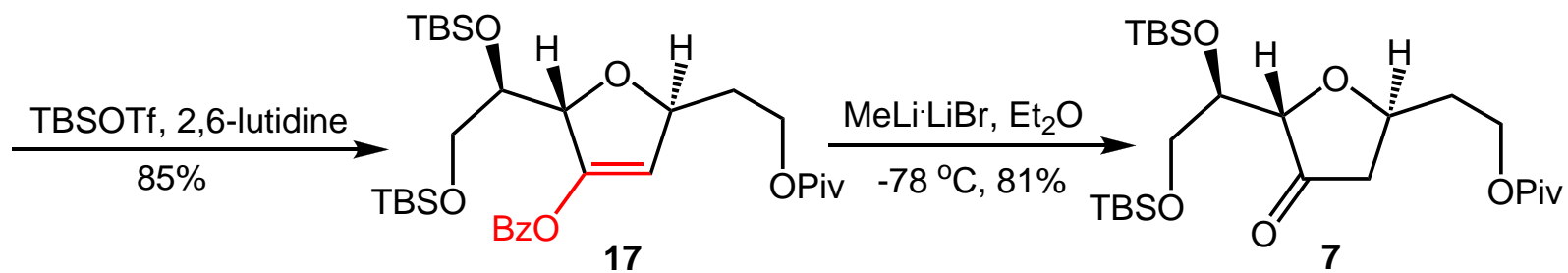
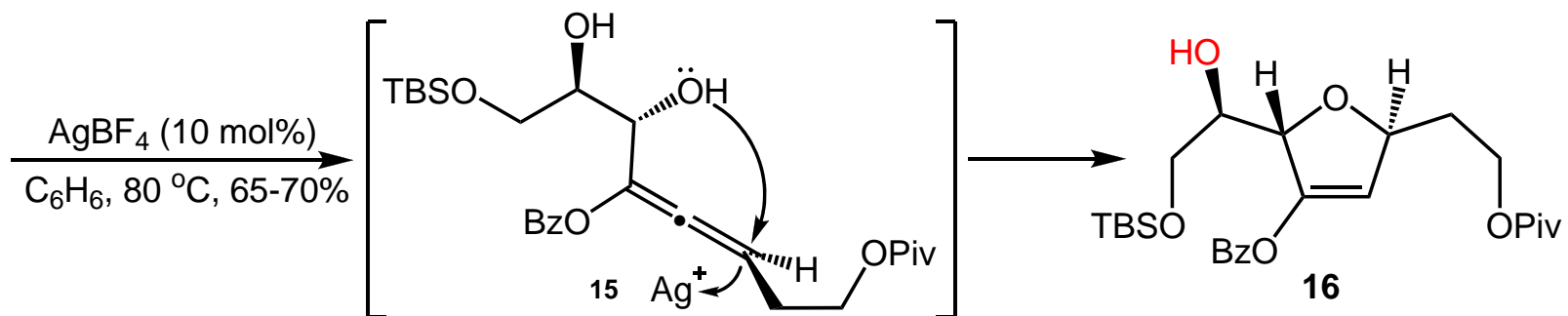
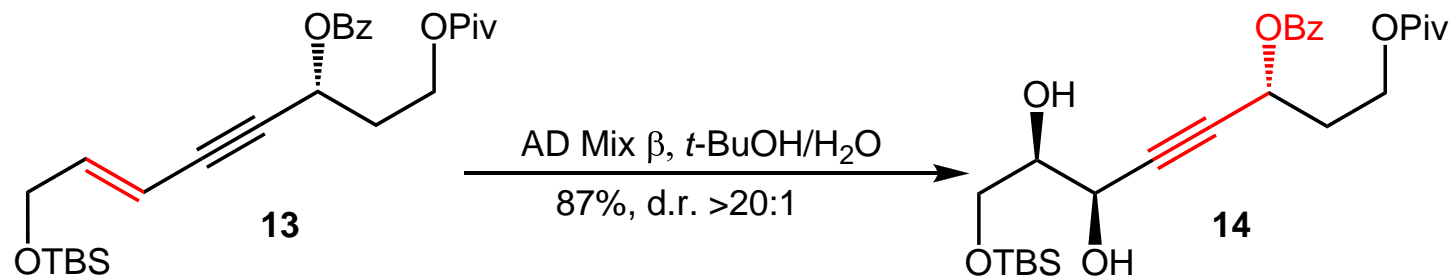


Retrosynthetic analysis of amphidinolide F.

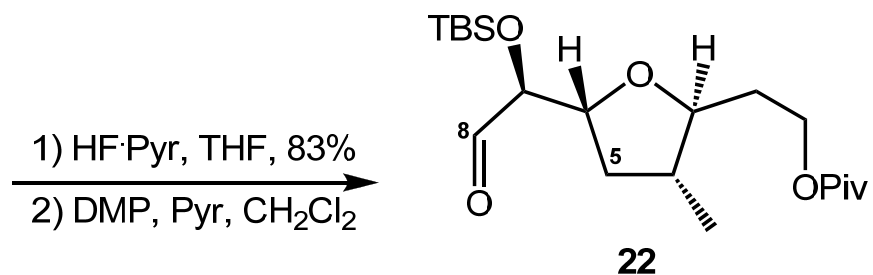
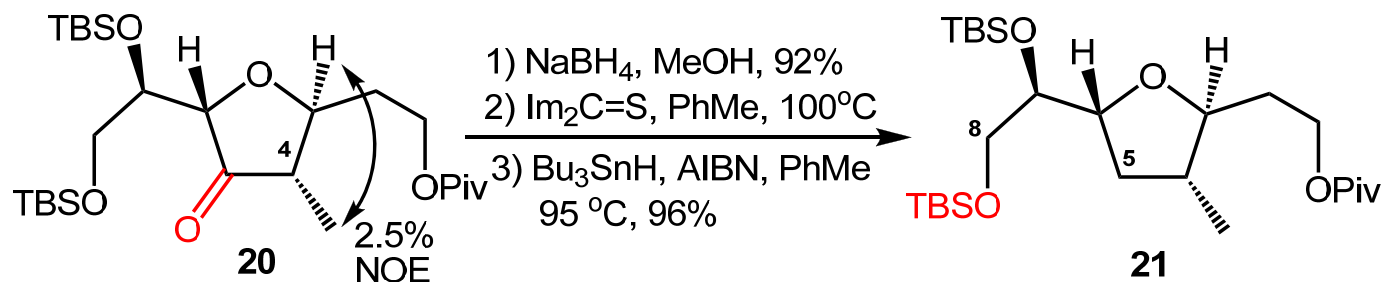
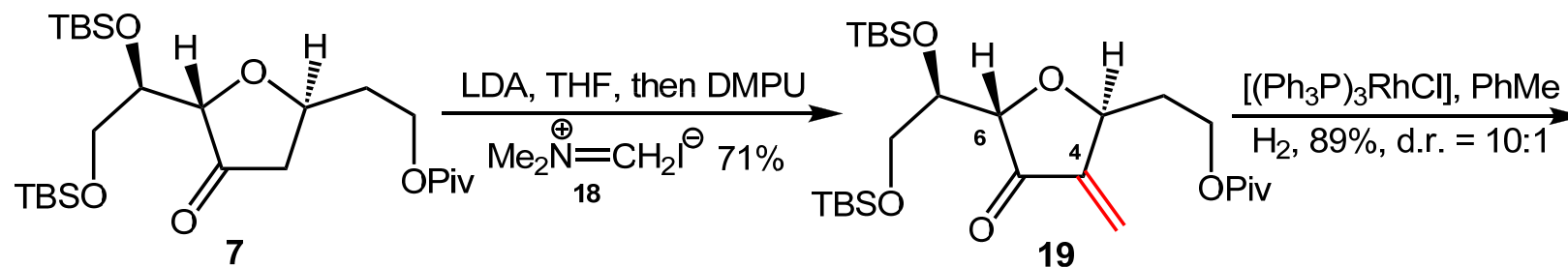


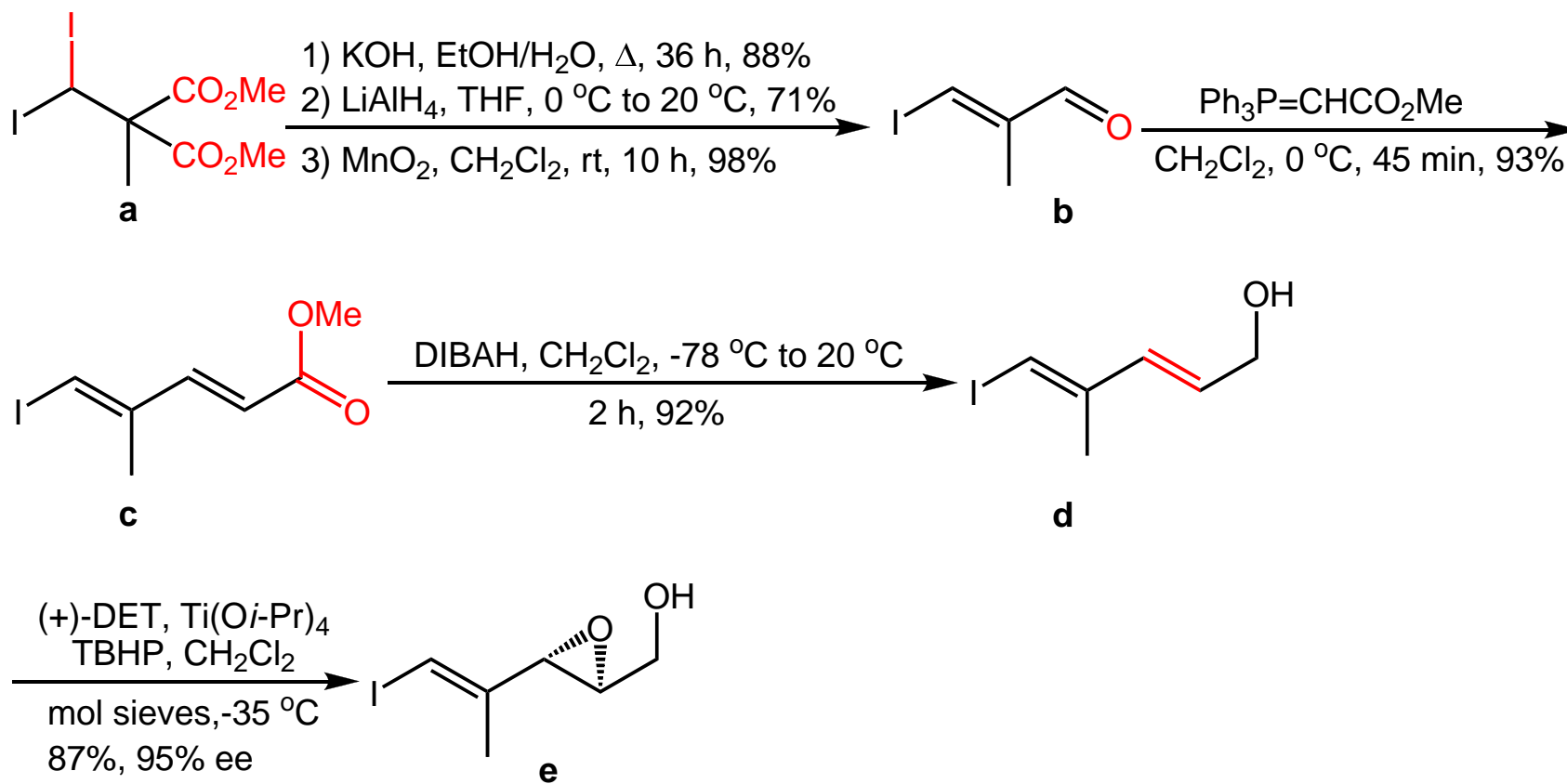
Synthesis of common intermediate

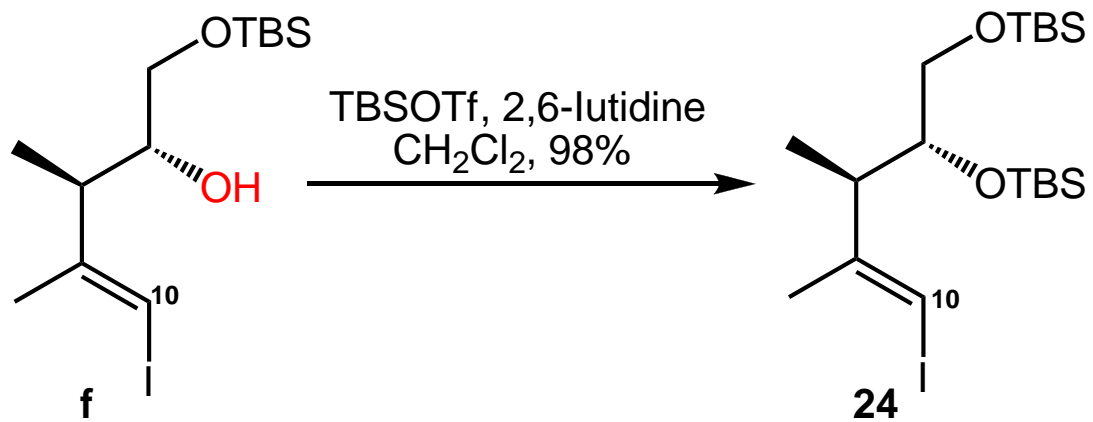
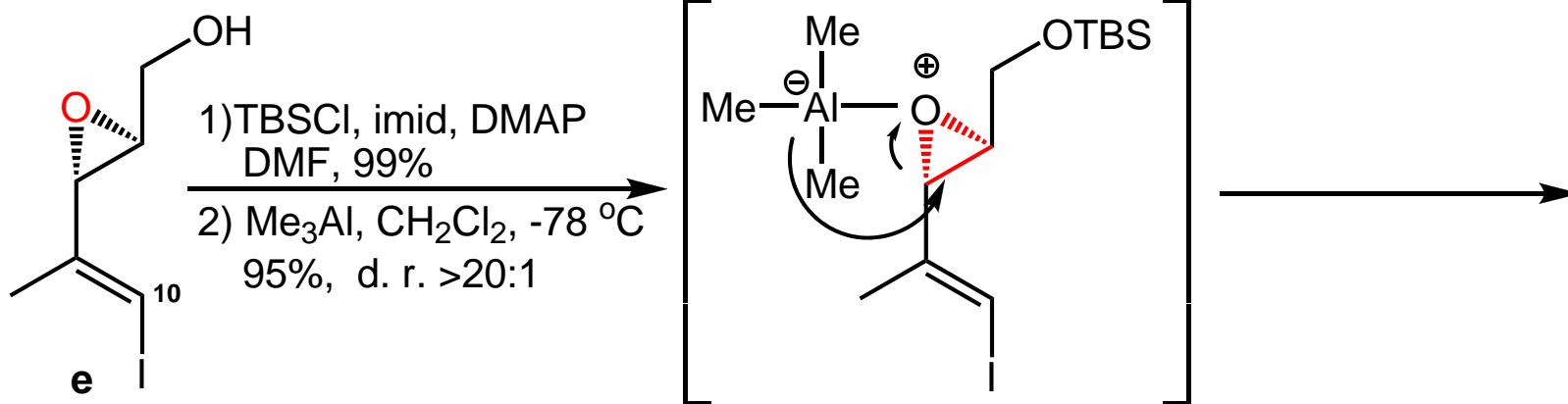


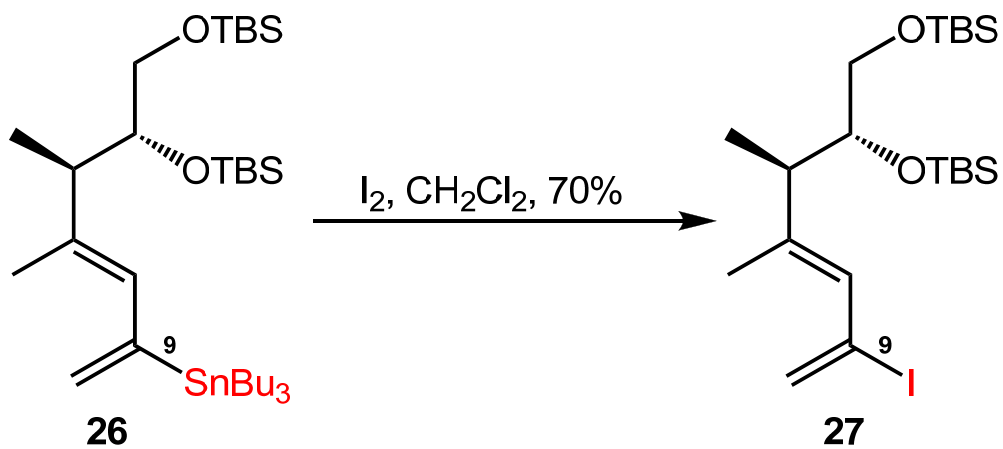
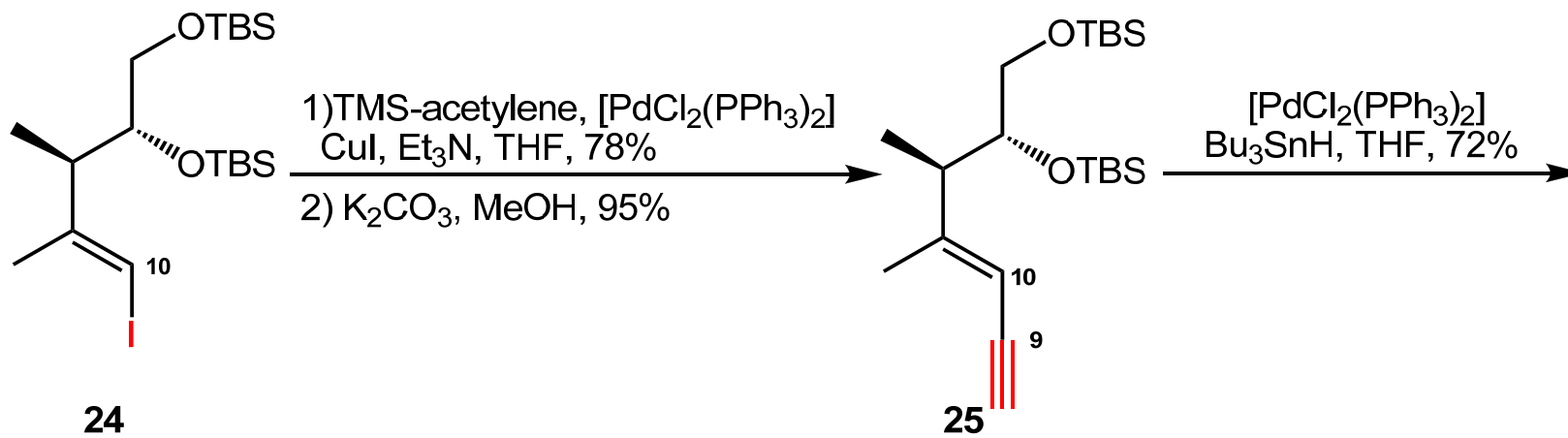


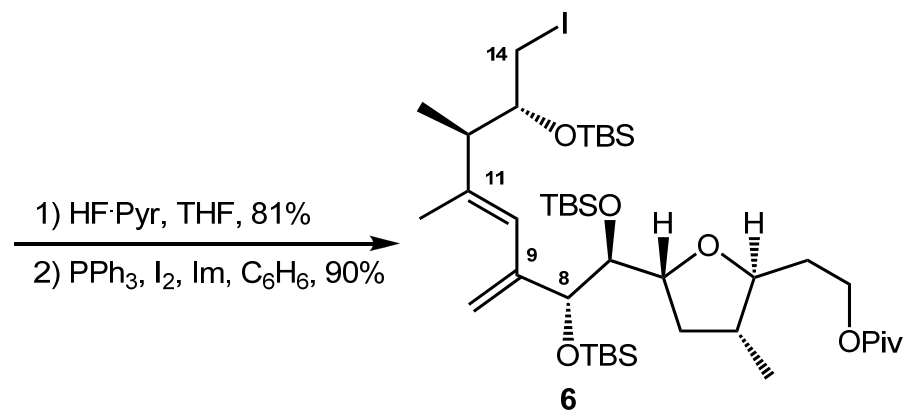
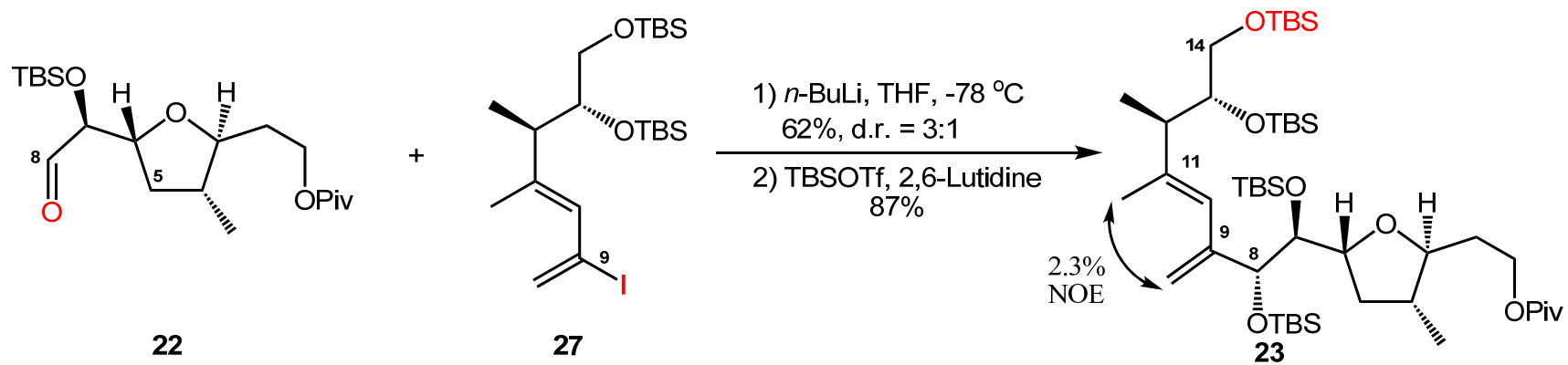
Synthesis of the C1-C14 subunit



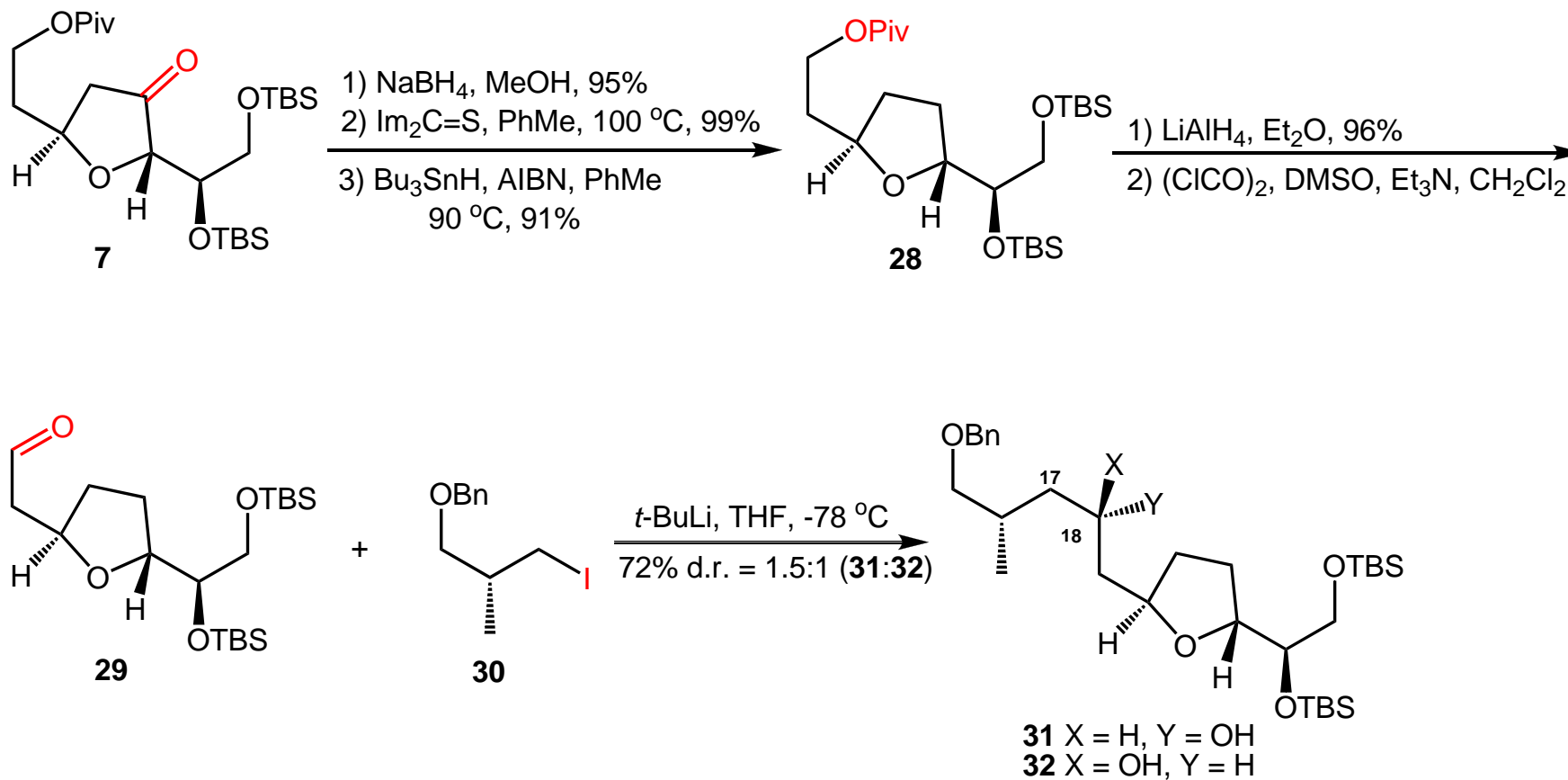


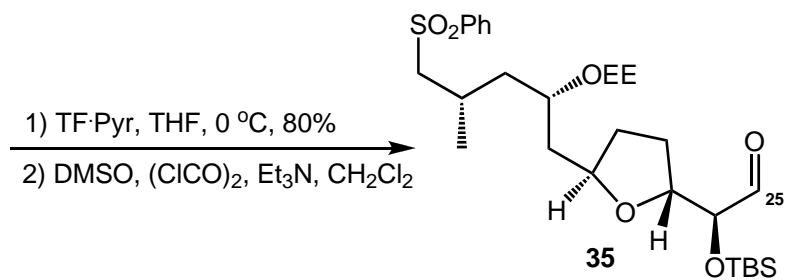
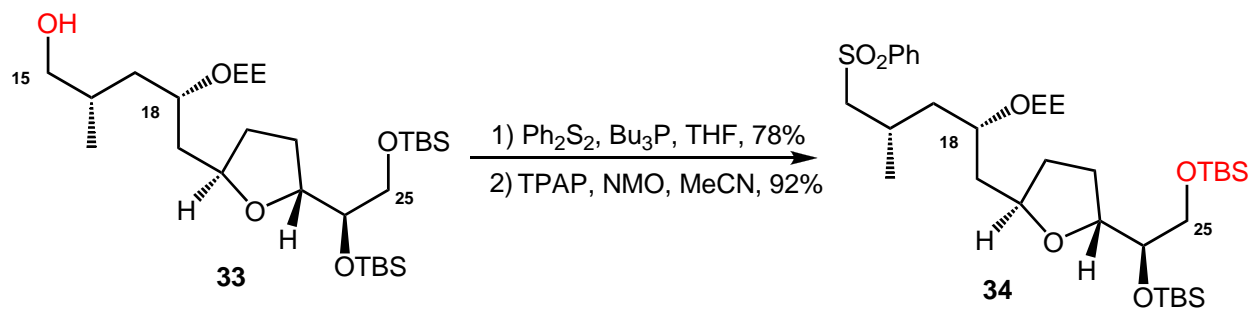
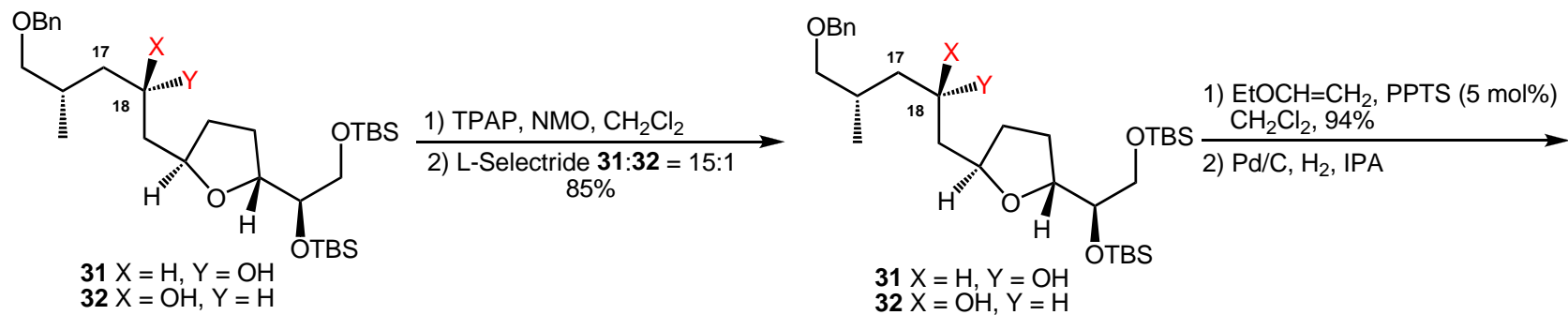


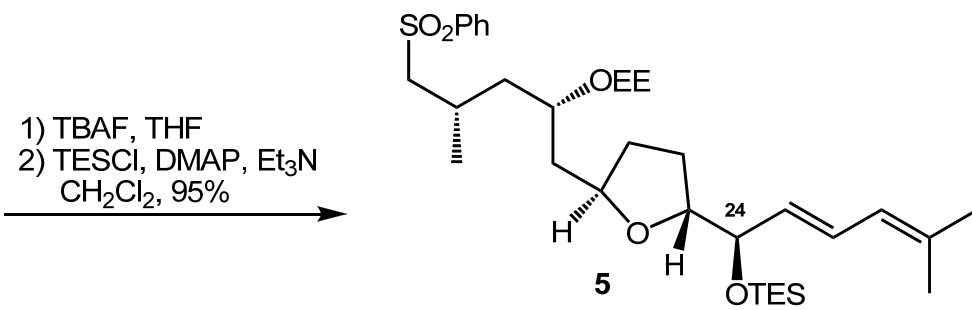
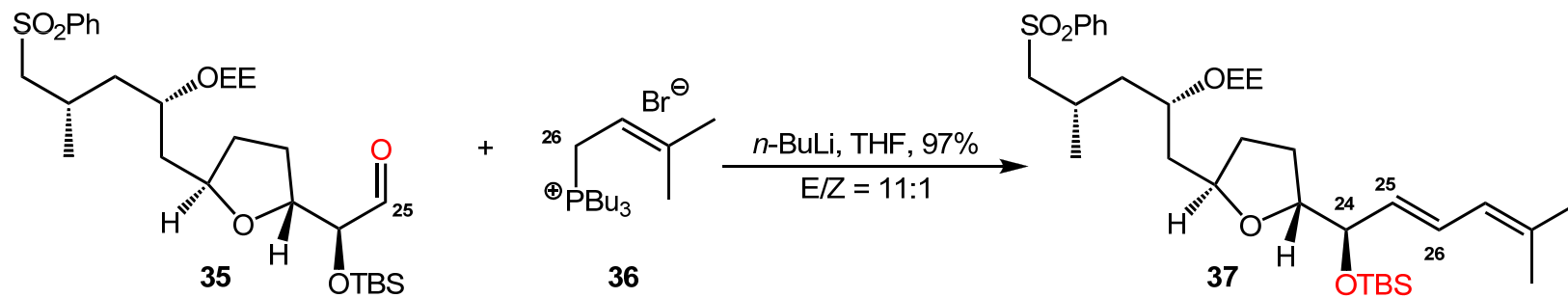




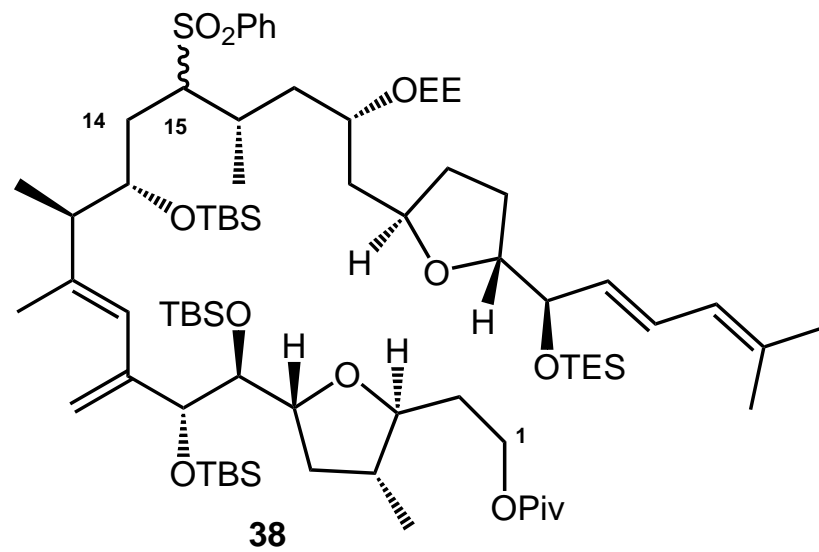
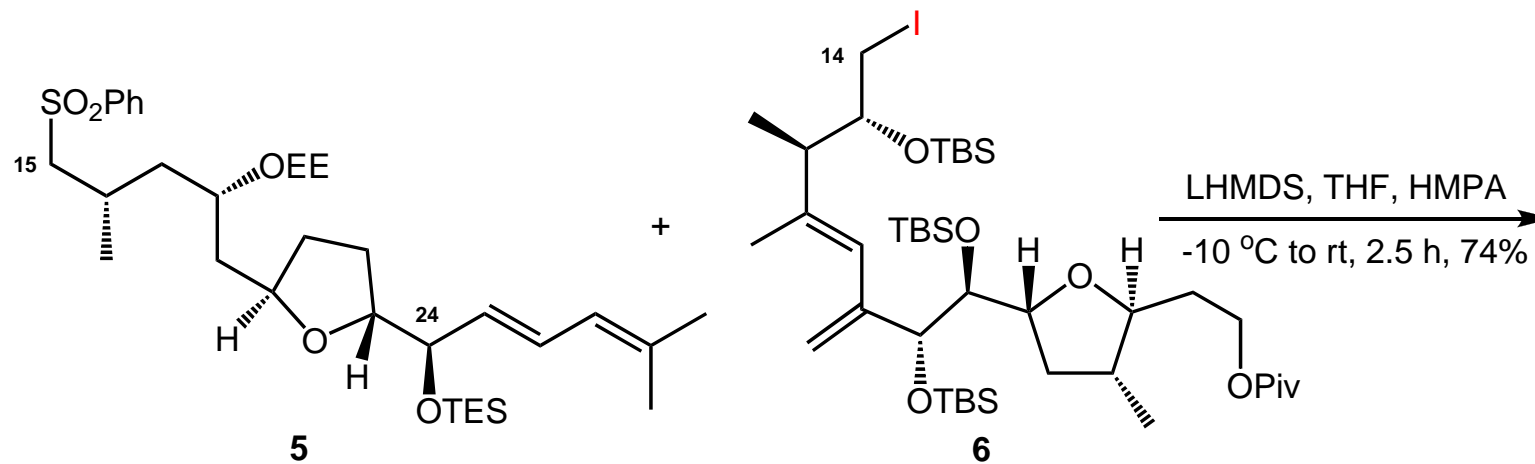
Synthesis of the C15-C29 subunit

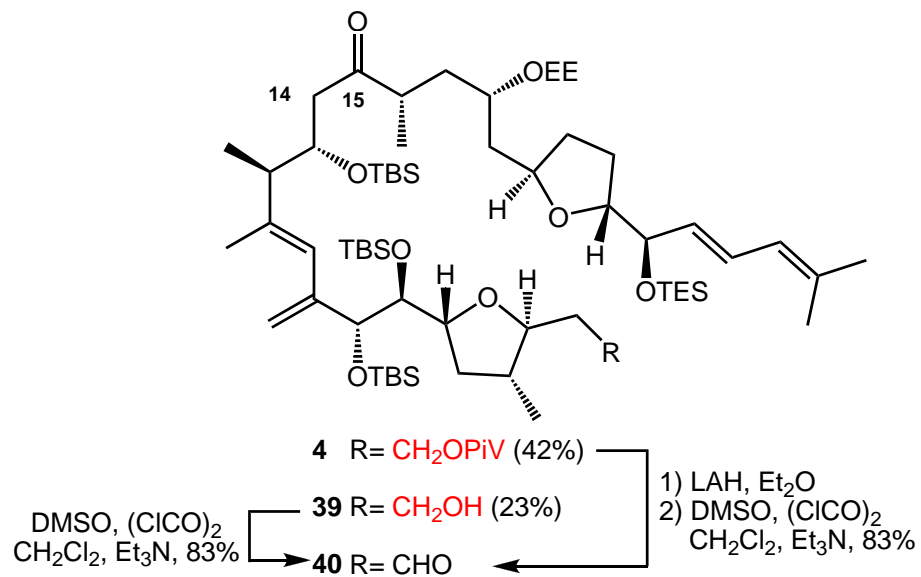
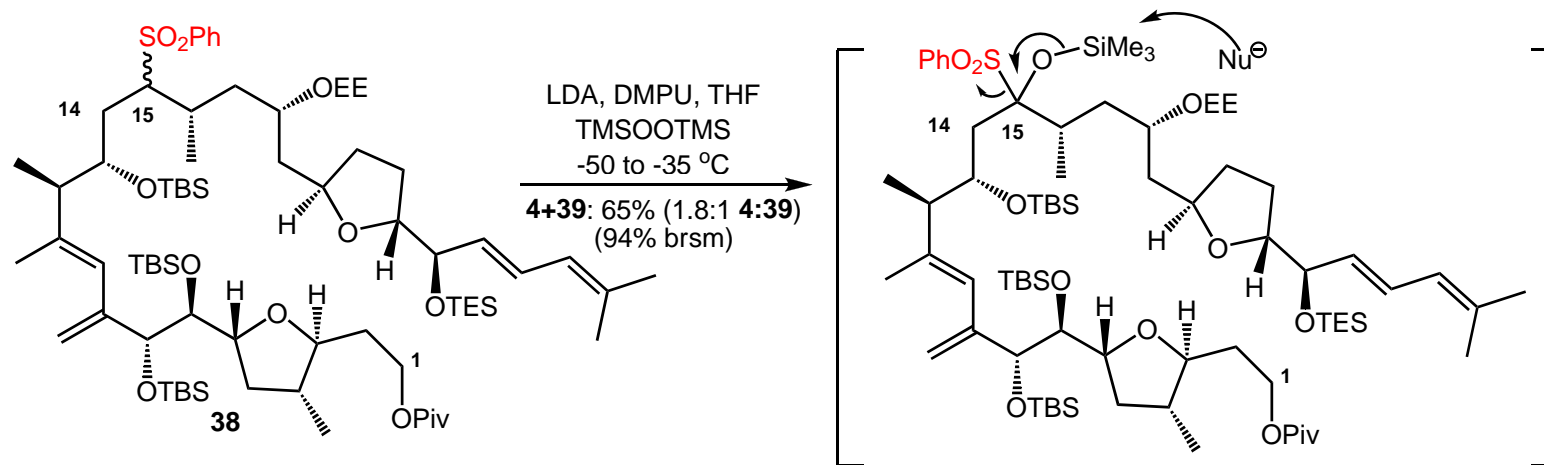


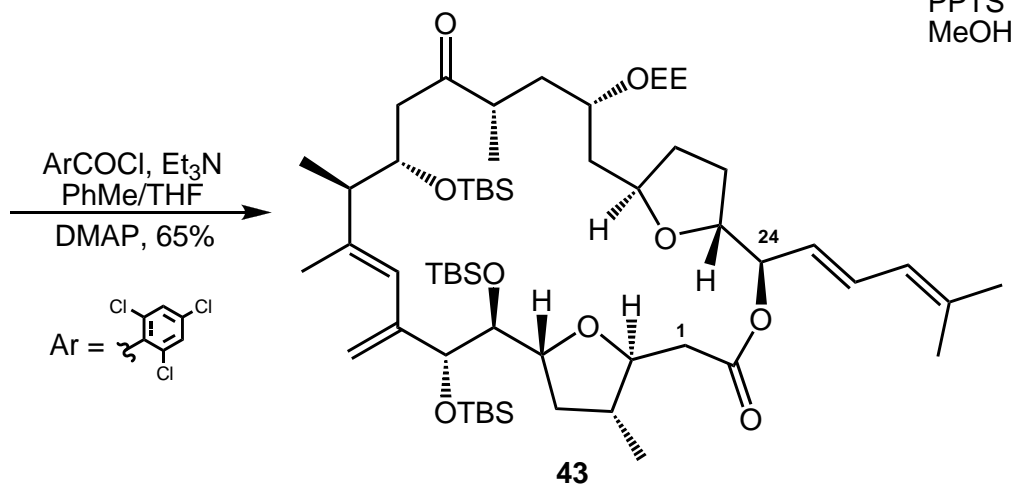
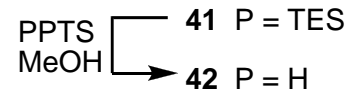
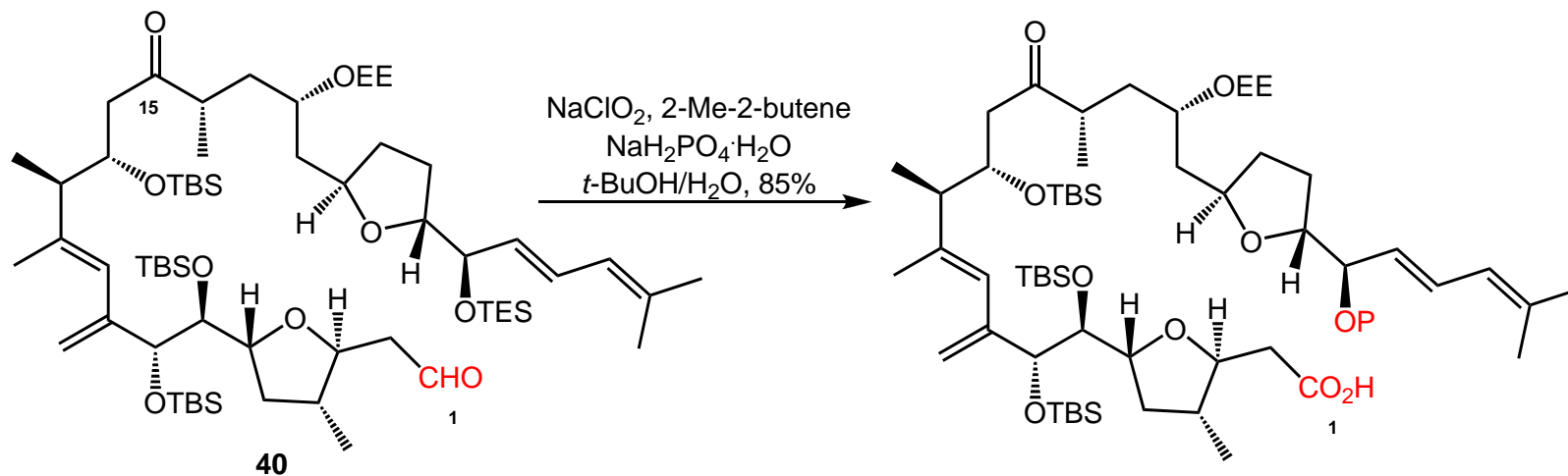


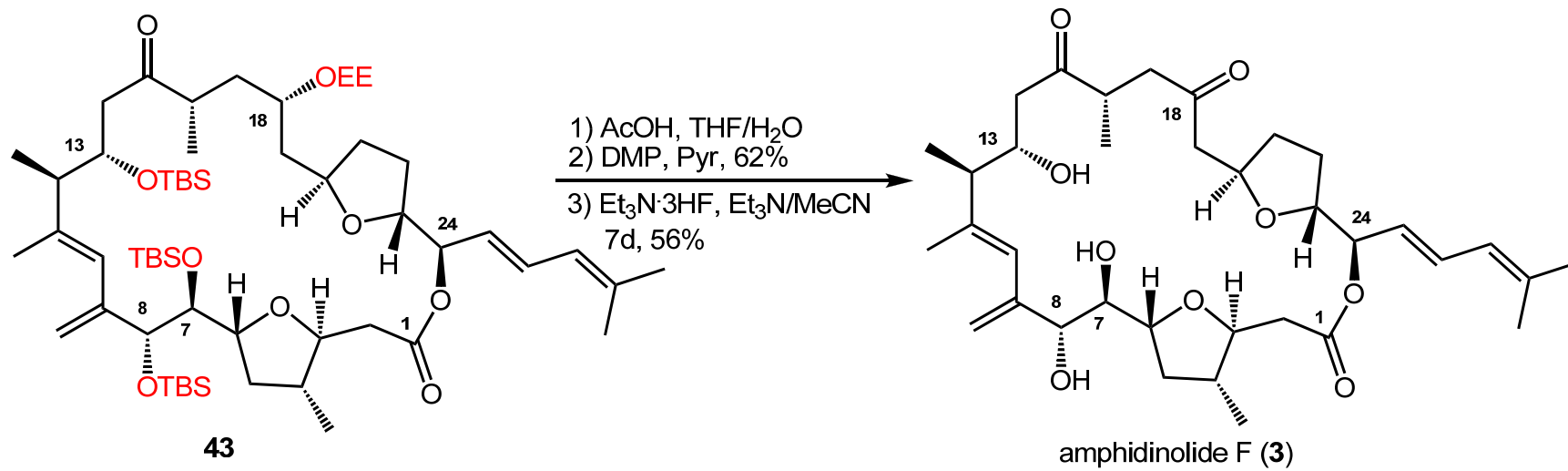


Total synthesis of amphidinolide F









Over 30 members of the diverse amphidinolide family of biologically active macrolides have been isolated from the dinoflagellate *Amphidinium* sp. From this family, amphidinolides C (**1–2**) and F(**3**) are among the most complex and densely functionalized members. These natural products **1–3** contain eleven stereogenic centers embedded within a 25-membered macrolactone including two *trans*-disposed tetrahydrofuran ring systems, a 1,4-diketone motif, and a highly substituted diene moiety at C9–C11. In addition to the sizable structural challenges present in **1–3**, these macrolides have shown significant cytotoxic activity. Consequently, compounds **1–3** have attracted considerable synthetic attention from numerous laboratories, including our own. Despite these sizable endeavors, neither amphidinolide **C** nor amphidinolide **F** have been successfully synthesized in the more than 20 years since their isolation. It should be noted that the stereochemical assignment of compound **3** is based on analogy to compound **1** and isolation from the same organism. Herein, we disclose the first total synthesis of amphidinolide F (**3**), and thus confirm both the absolute and relative stereochemistry of the natural product.

In summary, the total synthesis of amphidinolide F has been accomplished in 34 steps (longest linear sequence). Highlights of the synthetic sequence include a silver-catalyzed dihydrofuran formation, use of common intermediate **7** to access both the C1–C8 and C18–C25 fragments, regioselective hydrostannylation of enyne **25**, diastereoselective addition of a 2-lithio-1,3-diene species to aldehyde **22**, and the sulfone alkylation/oxidative desulfurization sequence to couple the major subunits and incorporate the carbonyl moiety at C15.
