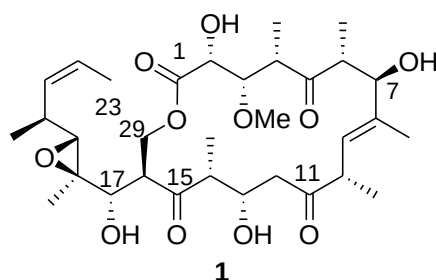


Total Synthesis of (+)-Tedanolide **1**

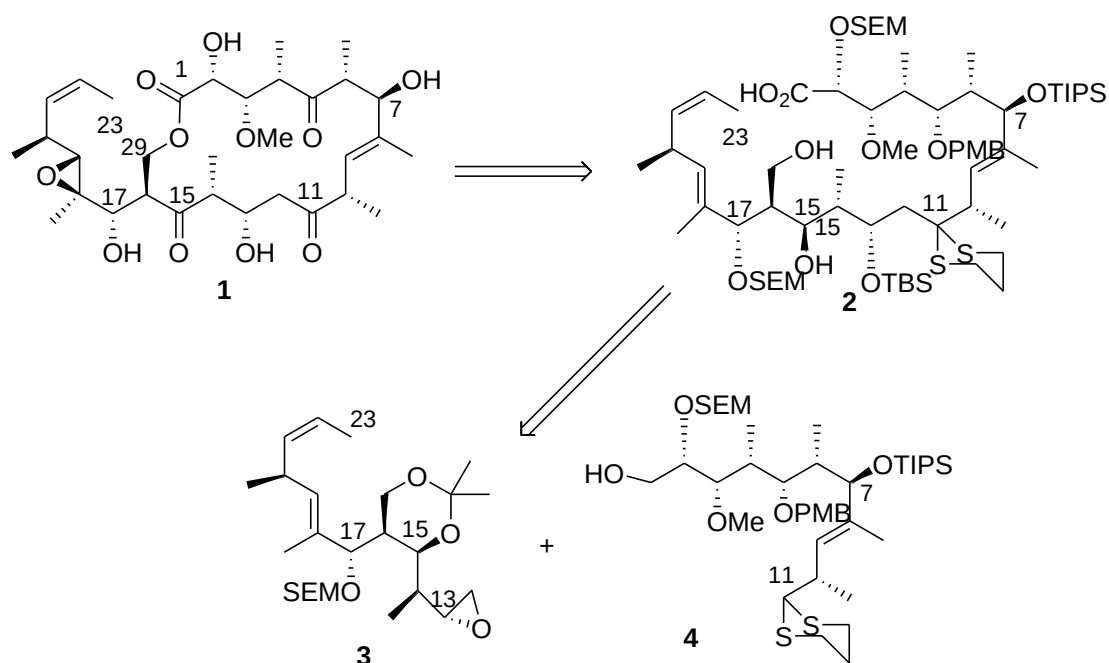
Tedanolide is a member of a small, architecturally intricate family of sponge metabolites. It displays exceptionally potent antitumor activities, increasing the life span of mice implanted with lymphocytic leukaemia by 23% at 1.5µg/kg of body weight.

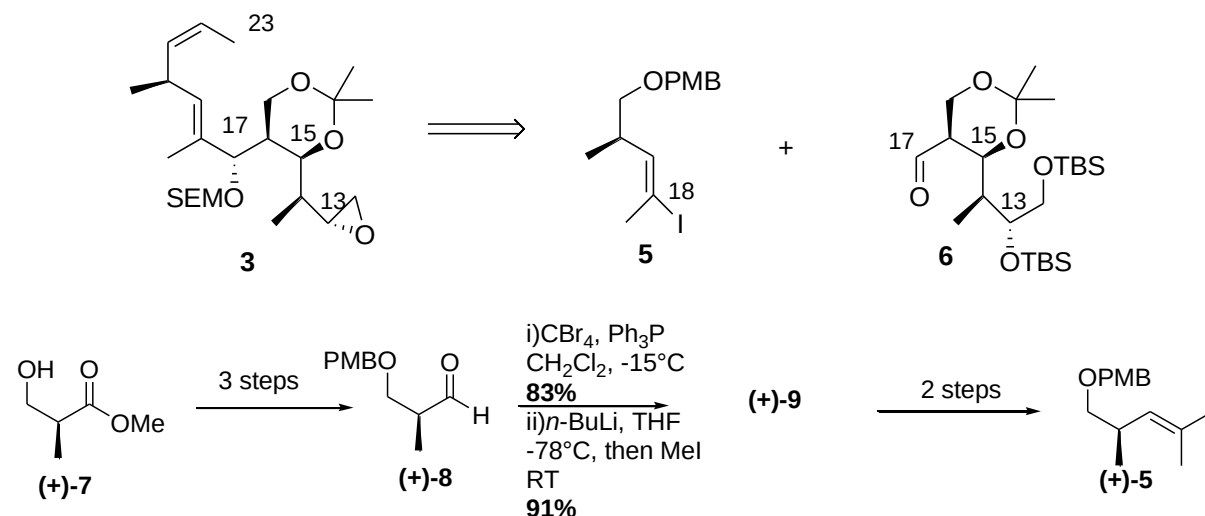
From the synthetic perspective, (+)-Tedanolide **1** comprises a significant challenge, given the four labile aldol units, a sensitive trisubstituted α -hydroxy epoxide, and a trisubstituted (*E*)-olefin encased in a 18-membered macrolide framework punctuated with 13 stereogenic centers.

Kalesse and co-workers achieved the first total synthesis of (+)-Tedanolide (**1**) exploiting a series of stereoselective aldol unions.

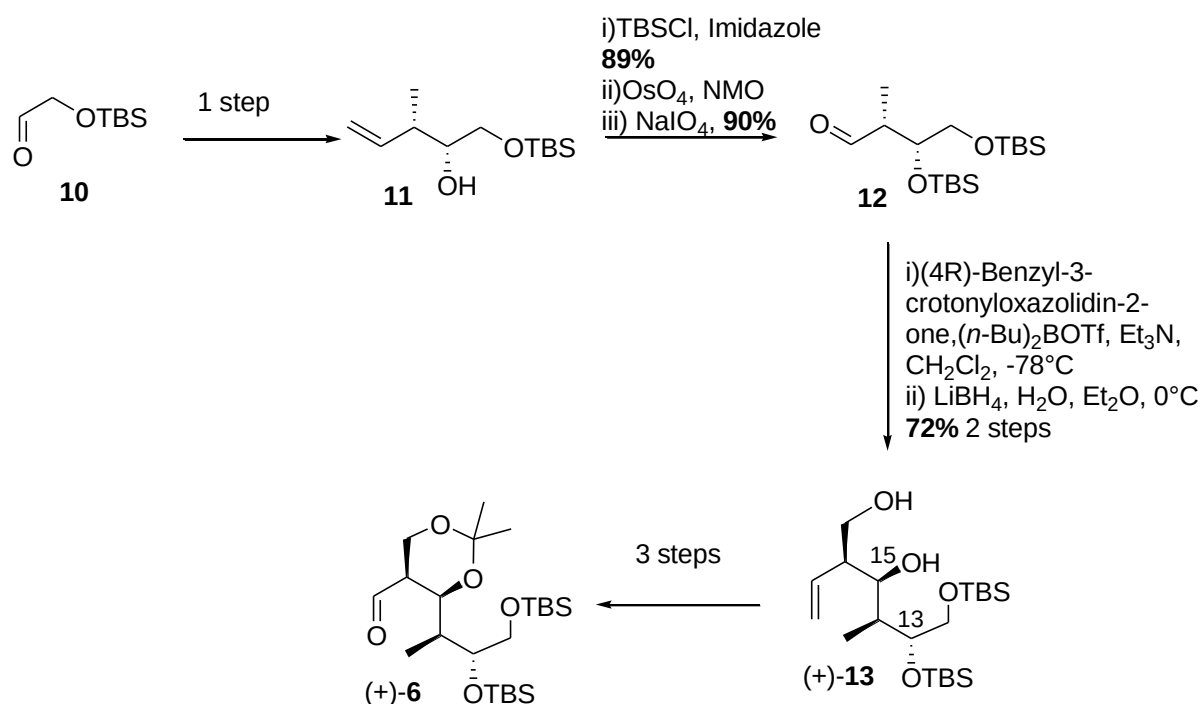
Synthetic analysis of (+)-Tedanolide (1)

The synthetic strategy called for initial construction of the macrocyclic domain, with stereoselective installation of the C(18,19) epoxide late in the synthetic sequence to avoid the need to carry this potentially unstable functionality through various synthetic steps. To this end, disconnection of (+)-tedanolide (**1**) at the macrolactone and C(11-12) linkage gave rise to known C(1-11) dithiane (-)-**4**^{1,2} and a C(13-23) epoxide **3**.

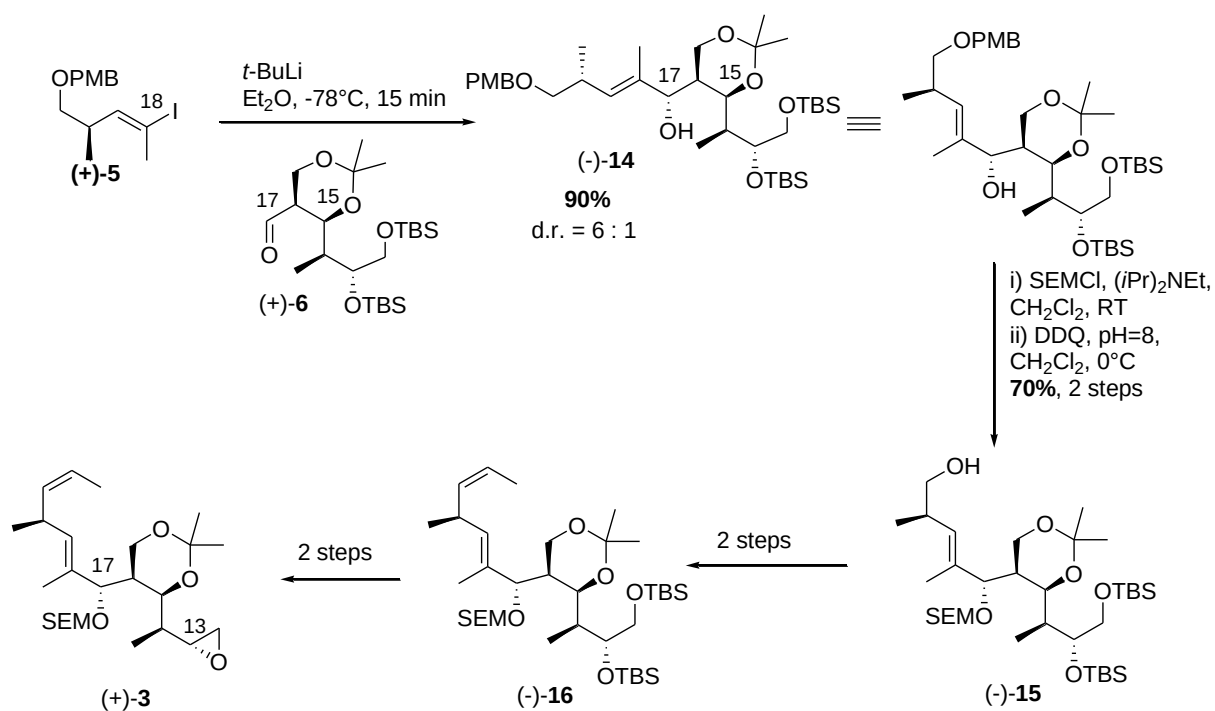


Synthesis of C(13-23) epoxide **3**

- 1) Give reagents for the synthesis of aldehyde (+)-8.
- 2) Give structure of (+)-9 and the name of this transformation.
- 3) Propose method for the formation of (*E*)-vinyl iodide (+)-5.



- 4) Propose reagents for the transformation **10** to **11** setting up two contiguous stereogenic centres.
- 5) Explain formation of homoallylic diol (+)-13.
- 6) Give reagents for the formation of aldehyde (+)-6.

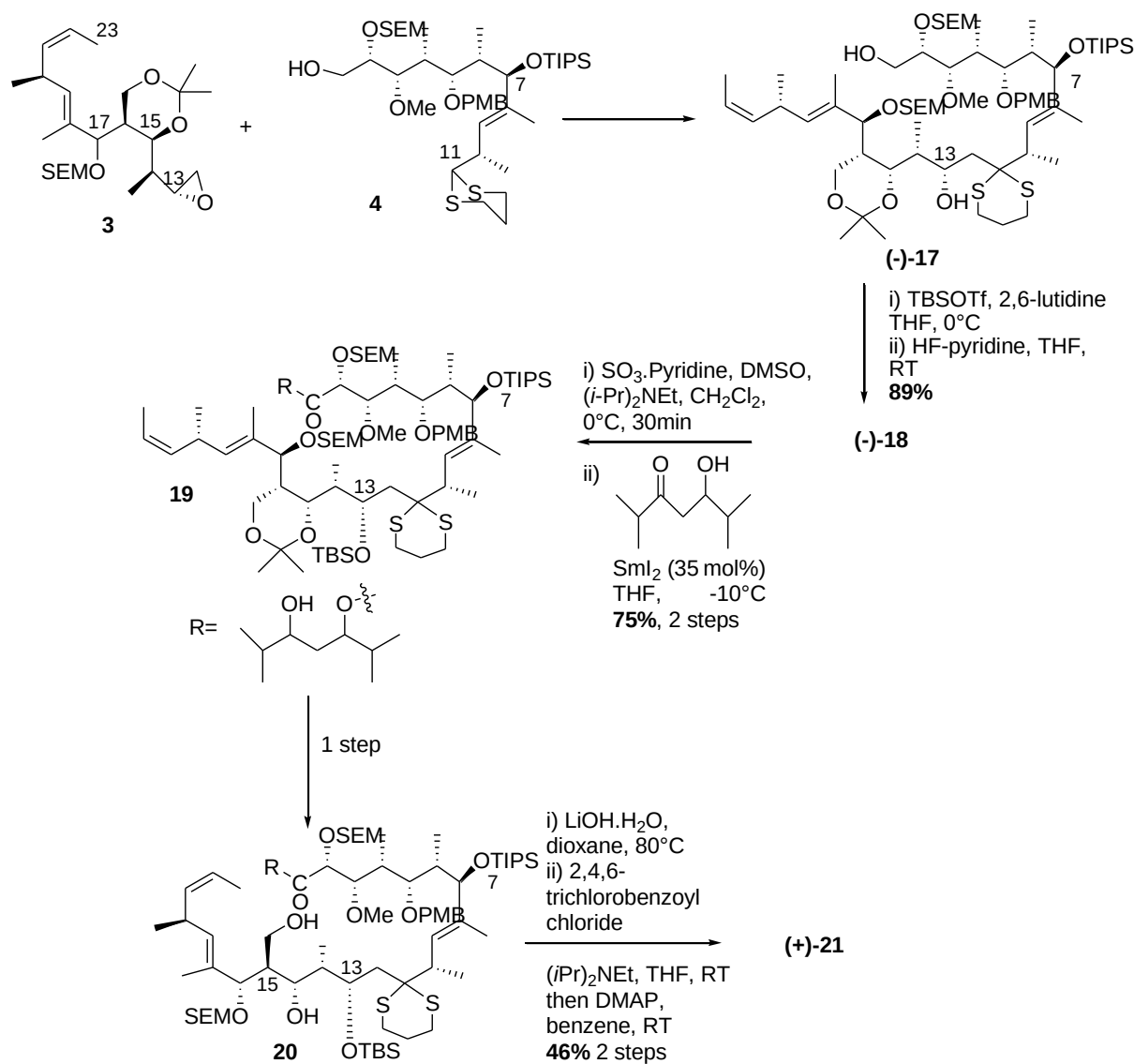


7) Explain the stereochemical outcome of the reaction 5 and 6 give 14.

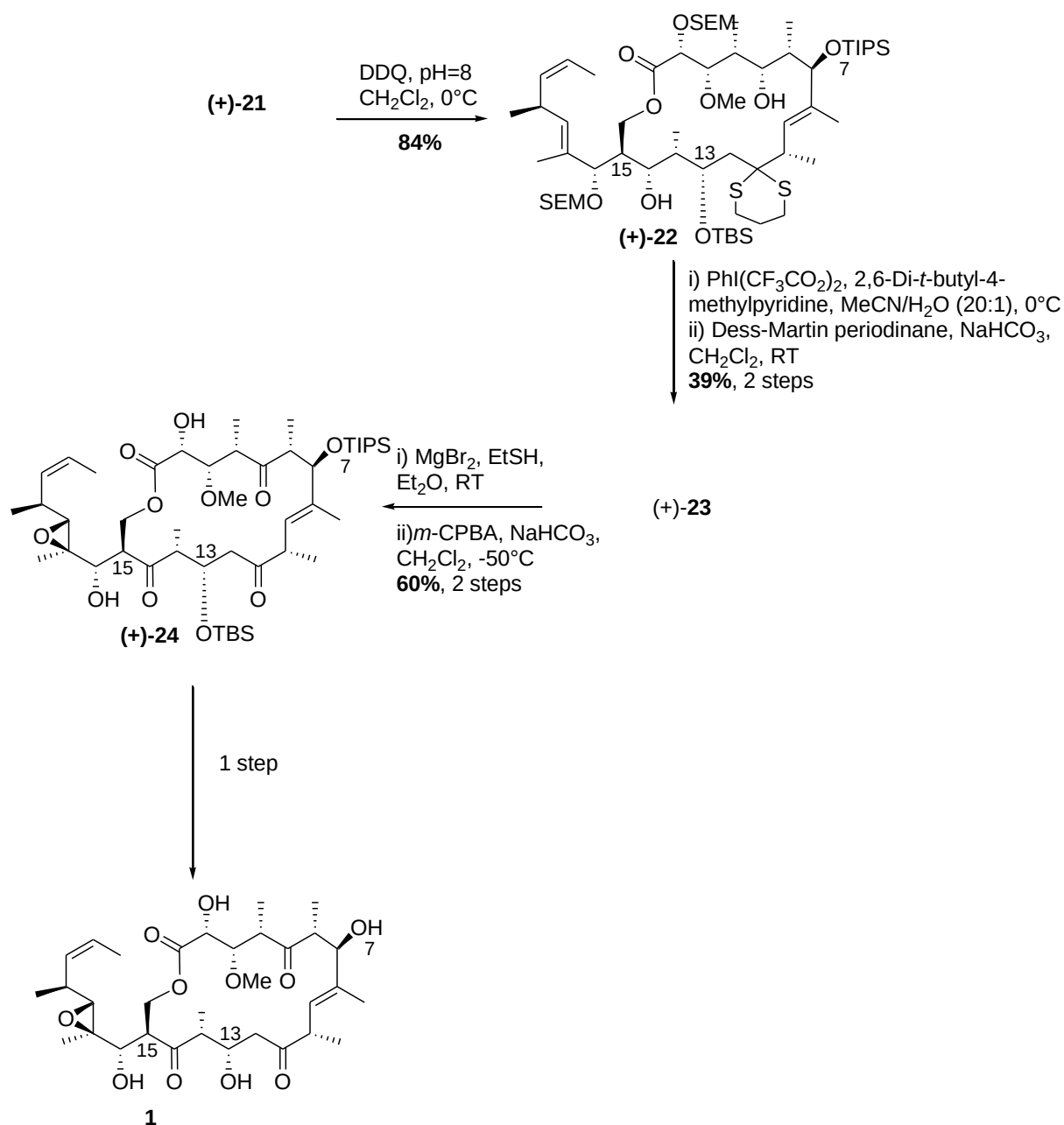
8) Give reagents for the formation of the (Z)-olefin 16.

9) Propose the 2 final steps to complete the synthesis of epoxide (+)-3.

Construction of the macrocycle



- 10) Which conditions would allow the union of the epoxide **3** and dithiane **4**?
- 11) Give structure of compound **18**.
- 12) Explain transformation **18** to **19**, what is the name of this reaction?
- 13) Give reagents for the formation of intermediate **20**.
- 14) Give structure of compound **21**.



15) Give structure of **23**. What is the name of the reaction step i.

16) Explain formation of **24**.

17) Give reagent for the formation of Tedanolide **1**.

References:

- Smith *J. Am. Chem. Soc.* **2005**, *127*, 6186
- Smith *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 12042