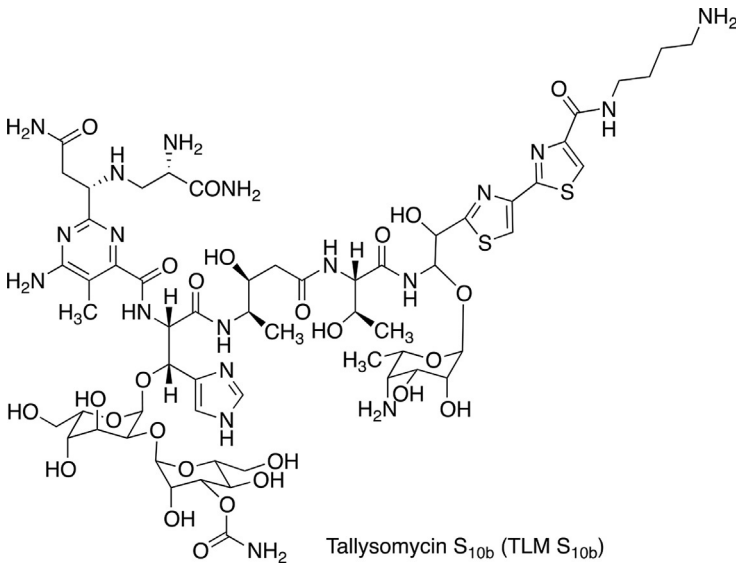
Tallysomycin S_{10b} (TLM S_{10b}) is another member of the bleomycin family that has reached clinical trials in patients with advanced head and neck tumors, showing a response similar to that of bleomycin A2.[86] Its high toxicity prompted the development of immunoconjugates for intracellular targeting (see Chapter 13, Section 4.6).



Tallysomycin S_{10b} (TLM S_{10b})

The bleomycins require a reduced transition metal, Fe(II) or perhaps Cu(I), oxygen, and a one-electron reductant to generate an "activated" bleomycin. The primary mechanism of action of the bleomycins is the generation of single- and double-strand DNA breaks and is initiated by the abstraction of a deoxyribose 4′-hydrogen. The species directly responsible for the removal of this hydrogen atom is an "activated" bleomycin complex **4.35**, arising from one-electron reduction of the bleomycin–Fe(II)–oxygen ternary complex. The electron may come from external reductors such as ascorbic acid or thiols or from another molecule of **4.34**, which would then be transformed into an inactive Fe(III) species **4.36**. Reaction of **4.35** with DNA involves abstraction of the ribose 4′-hydrogen and proceeds as previously discussed (see Figure 4.8). Finally, **4.33** can be regenerated from **4.36** by an NADH-dependent enzyme system in the nucleus or by reduction of external thiols, creating a cyclic process. This redox cycling (Figure 4.28) is important for bleomycin activity because only very small amounts of the drug enter the tumor cells due to its low lipophilicity.

A mechanism explaining the chemical details of the activation of the bleomycin ternary complex is shown in Figure 4.29. Addition of one electron and one proton to the bleomycin–Fe(II)–oxygen ternary complex **4.34** gives an Fe(III) hydroperoxo complex **4.37**, which has been detected experimentally by a variety of techniques.[87] One possible mechanism explaining the formation of the activated bleomycin species **4.35**, which is analogous to the one postulated for the case of heme-dependent enzymes such as cytochrome P450, involves the heterolytic cleavage of the O–O bond, initiated by a protonation step. This reaction gives a bleomycin–Fe(V)=O species **4.35** or its alternative Fe(IV) resonating form, which can abstract a hydrogen atom from DNA, initiating the series of events that culminate in strand cleavage.