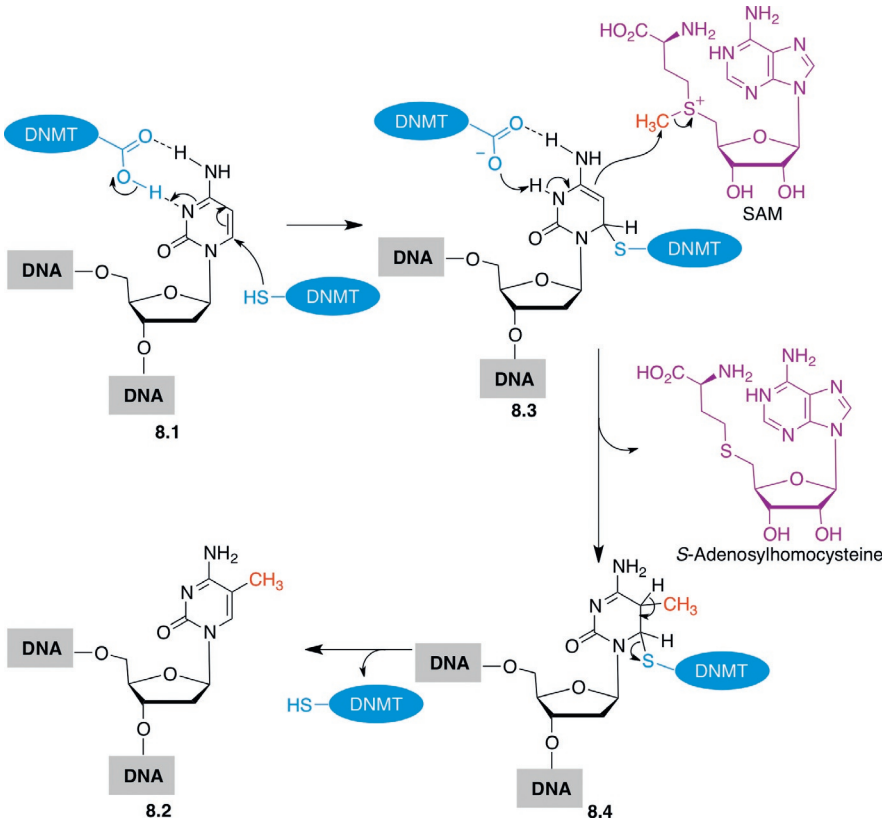

FIGURE 8.5

Mechanism of cytosine methylation by DNA methyltransferases.

Nucleoside inhibitors are converted by kinases and ribonucleotide reductases into deoxynucleotides that can be incorporated into DNA and complexed by the DNMT enzyme similarly to its natural substrates, allowing subsequent inhibition. Formation of covalent complexes with DNMTs results in enzyme depletion and, finally, a reversal of the methylation pattern.[10] In the case of decitabine, attack of the mercapto group in the active site to **8.5** gives adduct **8.6**, and its methylation at the N-5 position takes place normally to give **8.7**, but the lack of a hydrogen atom at N-5 after methylation prevents the elimination reaction necessary to restore the enzyme, which is thus inactivated (Figure 8.6).

5-Azacitidine[11] and its 2′-deoxy analog decitabine demonstrated the expected correlation between loss of methylation in specific gene regions and activation of the associated genes. Phase II clinical studies of 5-azacitidine as an antitumor drug took place in 1972, but its ability to inhibit DNA methylation was established in 1980. Beginning in 1993, a number of studies proved its efficacy in the treatment of myelodysplastic syndrome (MDS), leading to its approval by the U.S. Food and Drug Administration (FDA) in 2004 for this indication.[12] Decitabine is also a long-known anticancer drug that was tested in the clinic in the 1970s using the maximum tolerated doses, with myelosuppression as