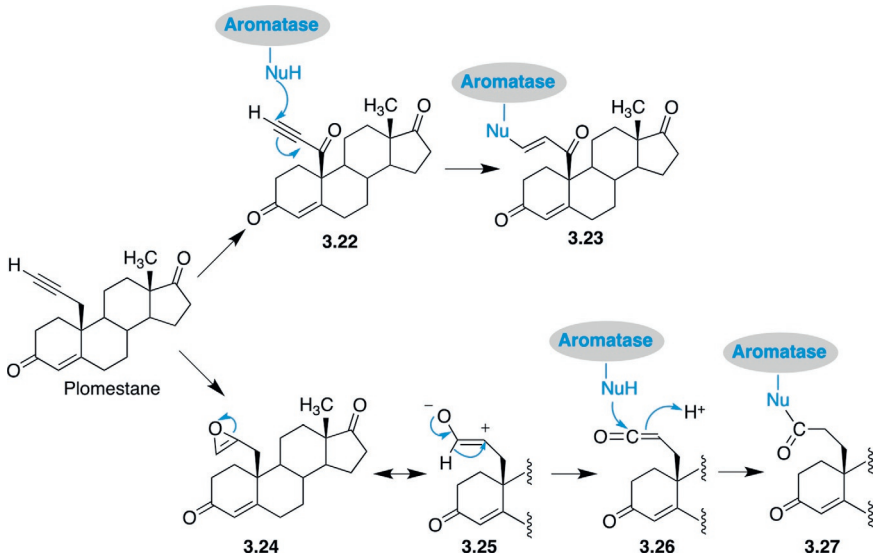

FIGURE 3.19

Aromatase inhibition by C-19 modified substrate analogs.

4.4 4-HYDROXYANDROSTENEDIONE DERIVATIVES

The main representative of this group is formestane (Lentaron®). This compound was first described as a competitive inhibitor, but subsequent evidence proved that its binding to aromatase was irreversible. The presence of the C-19 methyl group is essential because the 19-nor derivative is not an aromatase inactivator, which suggests that the 19-oxygenated metabolites are the inactivating species. The 4-hydroxy group is also essential, with the ethers and esters of formestane at O-4 being inactive. One possible mechanism that is consistent with these observations is summarized in Figure 3.20, although the low activity found for the intermediate formyl derivative **3.28** would seem to cast some doubt on this proposal.

Formestane is a second-generation steroidal aromatase inhibitor and the first one to reach clinical use during the early 1990s.[37] Its main drawback is that it must be administered intramuscularly in order to avoid its first-pass glucuronidation at the C-4 hydroxyl—a problem that renders it unsuitable for widespread clinical use.

4.5 STEROIDS WITH ADDITIONAL UNSATURATIONS AT THE A AND B RINGS

The first member of this class of compounds to be recognized as an aromatase inhibitor was testolactone. Subsequently were identified 1,4-androstadiene-3,17-dione and related compounds, including 1,4,6-androstatrien-3,17-dione (ATD) and 4-androstene-3,6,17-trione ("6-oxo"). Among other more