



FIGURE 3.16

Transformations catalyzed by aromatase.

Aromatase inhibition, especially by third-generation drugs, results in near complete estrogen deprivation. For this reason, some of the drugs discussed here have improved clinical outcomes compared to tamoxifen in breast cancer treatment due to the previously mentioned estrogenic agonistic effects of tamoxifen and to the genotoxicity of the metabolites of estradiol, especially its quinone derivatives.<sup>29</sup> AIs are now considered to be the standard treatment for postmenopausal women with hormone receptor-positive breast cancer. The combination of AIs and bisphosphonates to compensate their pro-osteoporotic effects has not been fully evaluated, and other possible long-term effects remain unknown.<sup>30,31</sup> A important drawback is that resistance to AIs inevitably occurs in metastatic settings after prolonged suppression of estrogen production.

#### 4.1 AROMATASE MECHANISM OF ACTION

Aromatase, also known as estrogen synthase, belongs to the group of microsomal cytochrome P450 enzymes responsible for hydroxylation metabolic processes. The overall process comprises a series of three oxidative steps. The first two are the insertion of two hydroxyl groups at the C-19 methyl group of its substrates leading to **3.9** and then to gem-diol **3.10**, which is dehydrated to aldehyde **3.11**. The third reaction is only partly understood, and it involves loss of the C-19 carbon atom as a molecule of formic acid, with concomitant aromatization of ring A.

One mechanistic possibility is that a third hydroxylation takes place at C-2 $\beta$ , yielding intermediate **3.12**, which would rearrange to **3.14** through the intermediacy of the cyclic hemiacetal **3.13**. Loss of a molecule of formic acid, driven by the generation of the aromatic A ring, would finally culminate the process, yielding the estrogens estradiol and estrone (Figure 3.17). However, experiments with isotopically marked **3.12** [2 $\beta$ -<sup>18</sup>O-, 19-<sup>3</sup>H]-2 $\beta$ -hydroxy-10 $\beta$ -formylandro-4-ene-3,17-dione] failed to show incorporation of  $\beta$ -hydroxyl to formic acid under enzymatic and nonenzymatic conditions.<sup>32</sup>