Tamoxifen, one of the most effective anticancer drugs ever, acts as an antiestrogen in breast tissue, blocking the activity of endogenous estrogens, most notably estradiol, at the estrogen receptor. There are a number of issues that limit tamoxifen's effectiveness related to the effects of tamoxifen in other tissues. Tamoxifen acts as an estrogen in the uterus, which increases the risk of uterine disorders involving growth of cells (proliferative action) in women taking the drug. In addition, tamoxifen's antiestrogen activity in the central nervous system can lead to hot flashes, one of the common complaints from women taking tamoxifen. Finally, breast cancer cells usually develop resistance to tamoxifen despite the fact that the majority of antiestrogen-resistant tumors remain ER-positive.

Biological Mechanism

The mechanism of action of tamoxifen is complex. Clearly, its principal mechanism of action is mediated by its binding to the estrogen receptor and the blocking of the proliferative actions of estrogen on mammary epithelium. One suggested mechanism for this antiproliferative action is the induction by
tamoxifen of the synthesis of the cytokine transforming growth factor-β (TGF-β), which acts as a negative autocrine regulatory molecule. However, it has also been shown that tamoxifen can induce synthesis of TGF-β in estrogen receptor-negative cells, such as fetal fibroblasts. Moreover, immunohistochemical studies have shown that tamoxifen induces the synthesis of TGF-β in the stromal (mesenchymal) compartment of breast cancers, suggesting a paracrine as well as autocrine mechanism of action, independent of an interaction with the estrogen receptor. Reports of some clinical efficacy of tamoxifen in the treatment of women with estrogen receptor-negative breast carcinomas would appear to be in accord with these mechanistic conclusions.

**Summary of Overall Synthetic Plan**

Starting with 2-phenyl-butyrophenone, a Grignard is applied to produce a tertiary alcohol, which is then treated with acid to form the intermediate (I). The addition of 2-(dimethylamino)-ethyl chloride treated with a base completes the reaction to produce cis, trans-tamoxifen.
Description of Individual Reactions

Step 1: The ketone 2-phenyl-butyrophenone is reacted with the Grignard agent 4-methoxyphenyl-magnesium bromide to form a tertiary alcohol (Figure I).

Step 2: A concentrated acid (HCl) is used to remove the CH₃ from the oxygen attached to the ring. This is done by Cl⁻ that attacks the carbon. The electrons are pushed onto the ring, making the ring with the oxygen and the ring’s other substituents a good leaving group. H⁺ ion protonates the OH group, making a H₂O group (a good leaving group.) The H₂O leaves and the electrons are pushed into a carbon-carbon double bond. The result is figure II.
Step 3: The molecule is reacted with 2-(dimethylamino)-ethyl chloride using a base (NaOC₂H₅) in a Sn₂ reaction to produce the cis, trans-tamoxifen.
Annotated Bibliography

Structure illustration of tamoxifen:

Medical use:
Rickert, Emily L.; Trebley, Joseph P.; Peterson, Anton C.; Morrell, Melinda M.; Weatherman, Ross V., “Synthesis and Characterization of Bioactive Tamoxifen-conjugated Polymers.” Department of Medicinal Chemistry and Molecular Pharmacology and the Purdue Cancer Center, Purdue University, 575 Stadium Mall Drive, West Lafayette, Indiana 47907. National Institutes of Health Public Access.

Mechanism of Action:

Synthesis Scheme