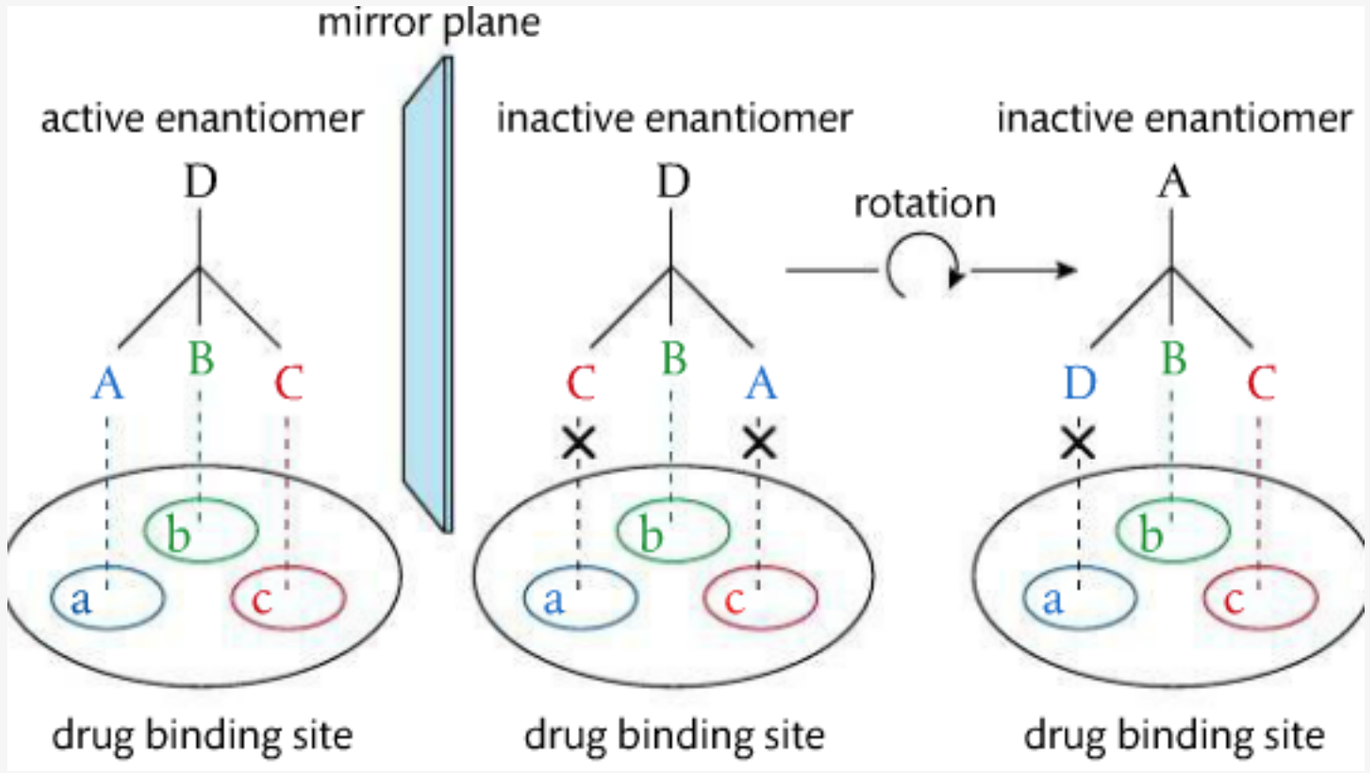
Option D: Medicinal Chemistry

Part D.7

D.7 Taxol: a chiral auxiliary case study

- Remember enantiomers?
- Your body is a chiral environment that reacts differently with enzymes and receptors



D.7 Taxol: a chiral auxiliary case study

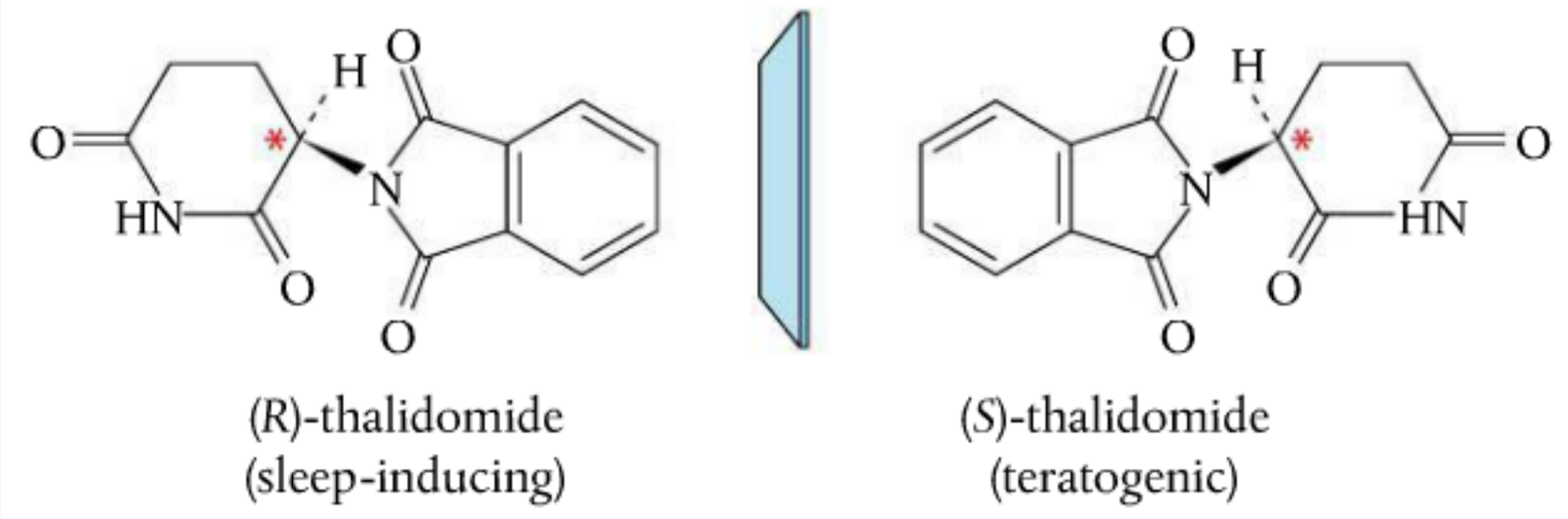
Biology vs. Chemistry

- **in vivo** - biological synthesis reactions within cells - produce only one enantiomeric form
  - when a drug is harvested from a natural source (morphine from opium) - single enantiomer
- **in vitro** - when drugs are produced outside the body - they yield a mix of enantiomers (*racemate*)

D.7 Taxol: a chiral auxiliary case study

Thalidomide Tragedy

- Sleep inducing drug (for pregnant women) manufactured and sold as a racemic mixture
- (R) isomer had the desired effect, (S) isomer was discovered to be teratogenic - caused serious fetus deformities



D.7 Taxol: a chiral auxiliary case study

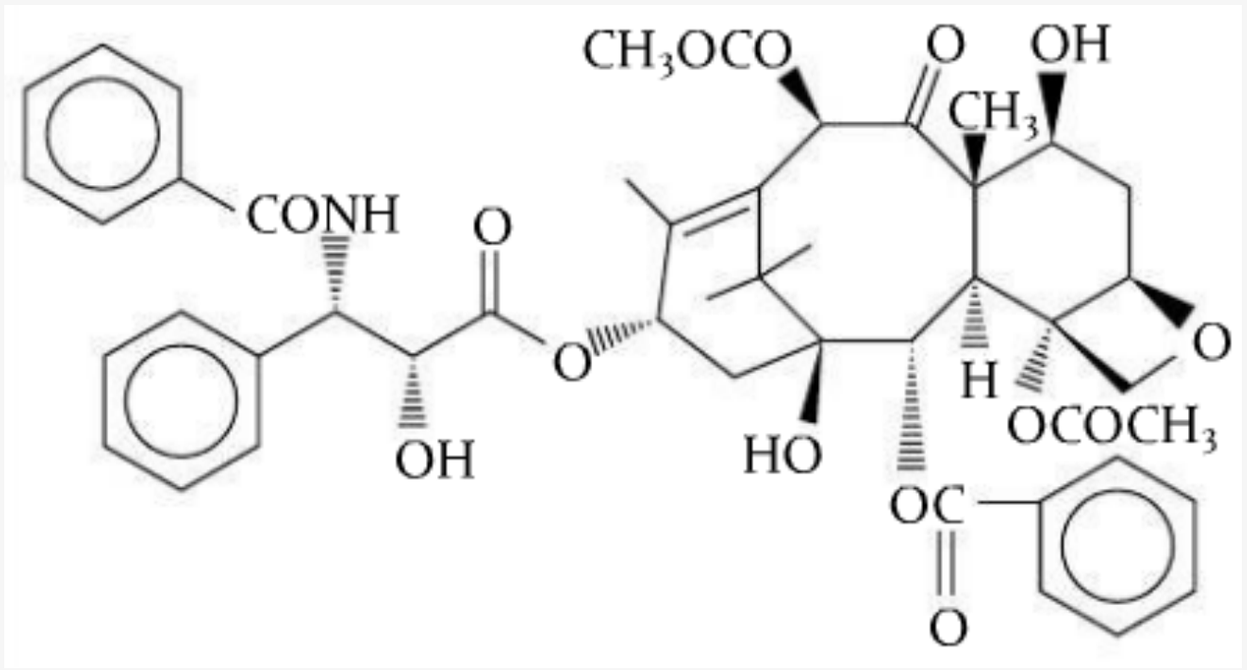
Racemic Drugs?

- Ibuprofen and Prozac are marketed as racemic drugs
- No regulatory mandate to create single enantiomer drugs - becoming more common
- about 50% of drugs on the market are single enanatiomer (the other half are racemic)
- Single enantiomeric drug development of Taxol…

D.7 Taxol: a chiral auxiliary case study

Taxol - the anti-cancer drug

- Taxol (aka Paclitaxel) has potent effect against solid tumors and was approved for chemotherapeutic use in 1992
- Primarily used in treatment of breast and ovarian cancer

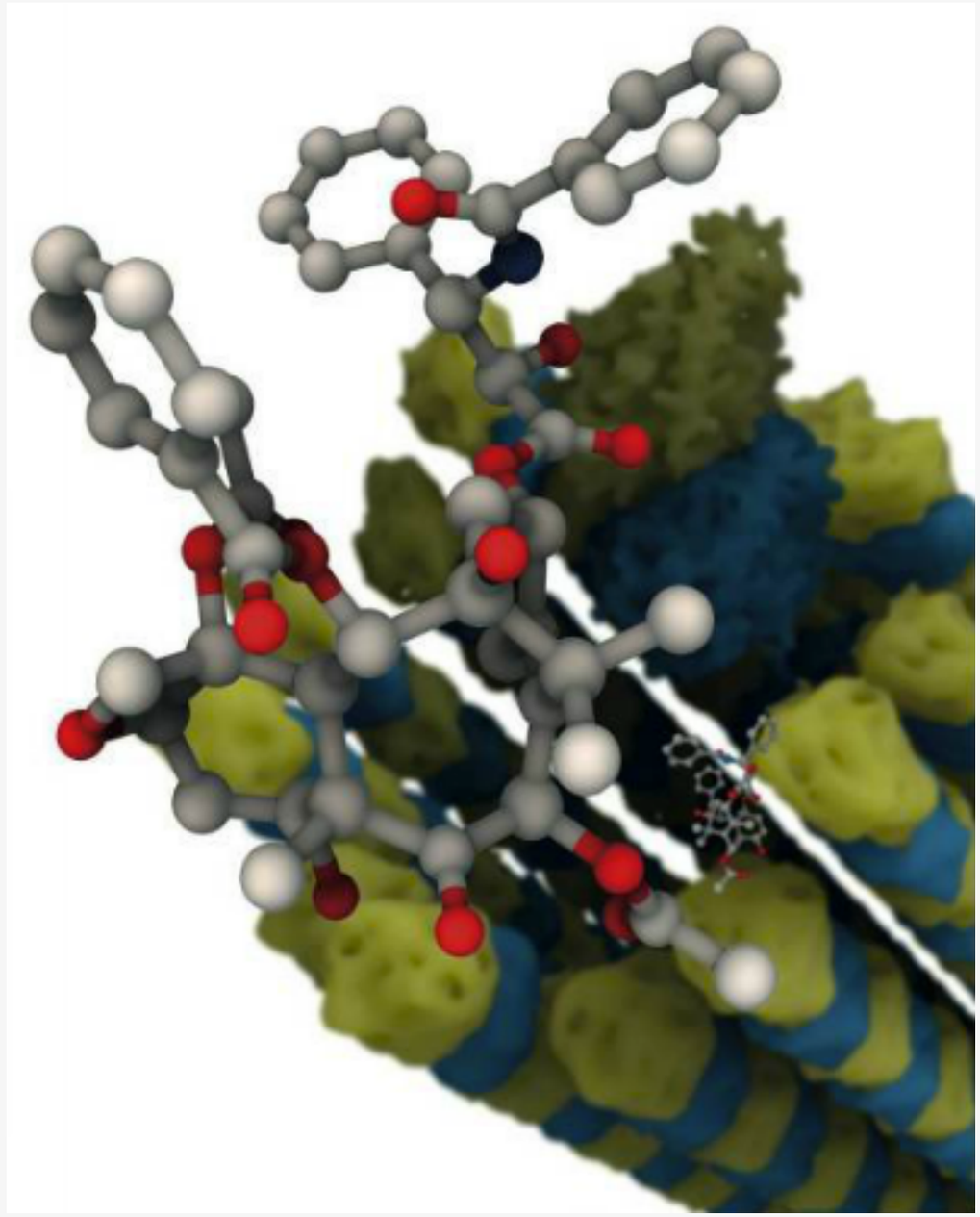


Taxol - can you find the 11 chiral carbons?

D.7 Taxol: a chiral auxiliary case study

Taxol's anti cancer properties

- Taxol can bind to **tubulin** (protein) in cells, which is the main component of **microtubules** which form spindles during cell division
- When Taxol binds @ microtubules - prevents spindles from breaking down and stopping cell division
    - Prevents growth of the tumor



D.7 Taxol: a chiral auxiliary case study

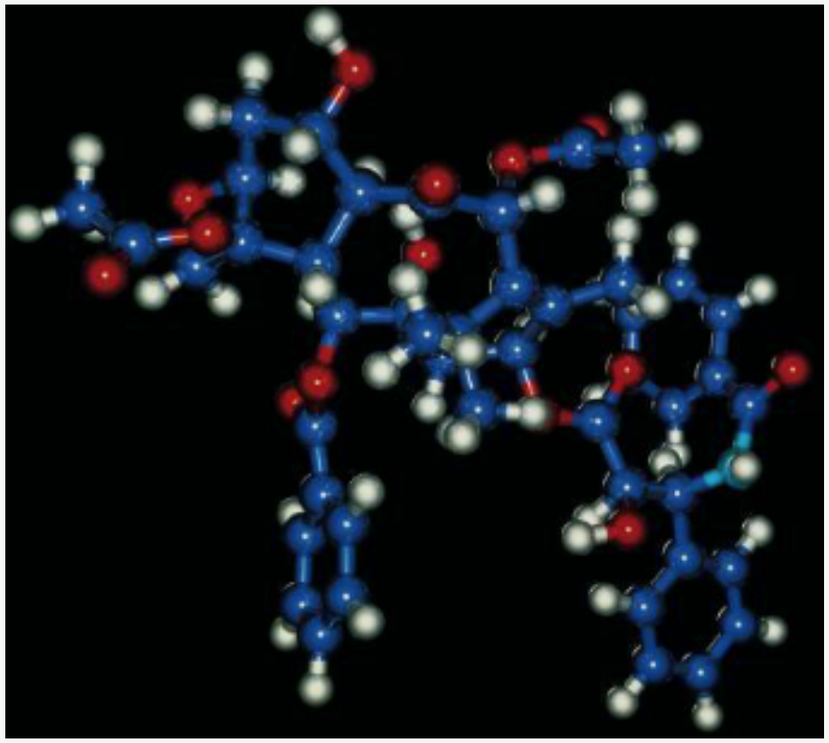
Finding Taxol Naturally

- First isolated from the bark of the pacific yew tree
- Bark - contains 0.0004% Taxol - need LOTS of bark
- When bark is harvested, it kills the tree, which take 200 years to mature and are vital part of the ecosystem
- Caused the effort to synthesize the drugs and its analogues

D.7 Taxol: a chiral auxiliary case study

Asymmetric Synthesis

- Major challenge of drug design - 11 chiral centers in Taxol
- Isolating the desired enantiomer from the racemic mixture is wasteful as much of the product is wasted
- Pharmaceutical companies will use asymmetric synthesis (aka enantioselective synthesis)



D.7 Taxol: a chiral auxiliary case study

Chiral Auxiliary…

- A chiral molecule that binds to the reactant, physically blocking one reaction site through steric hindrance
- This ensures that the next step in the reaction can take place from only one side, forcing the reaction to proceed with a specific stereochemistry
- Once the enantiomer has been set, the auxiliary can be taken off the molecule and recycled

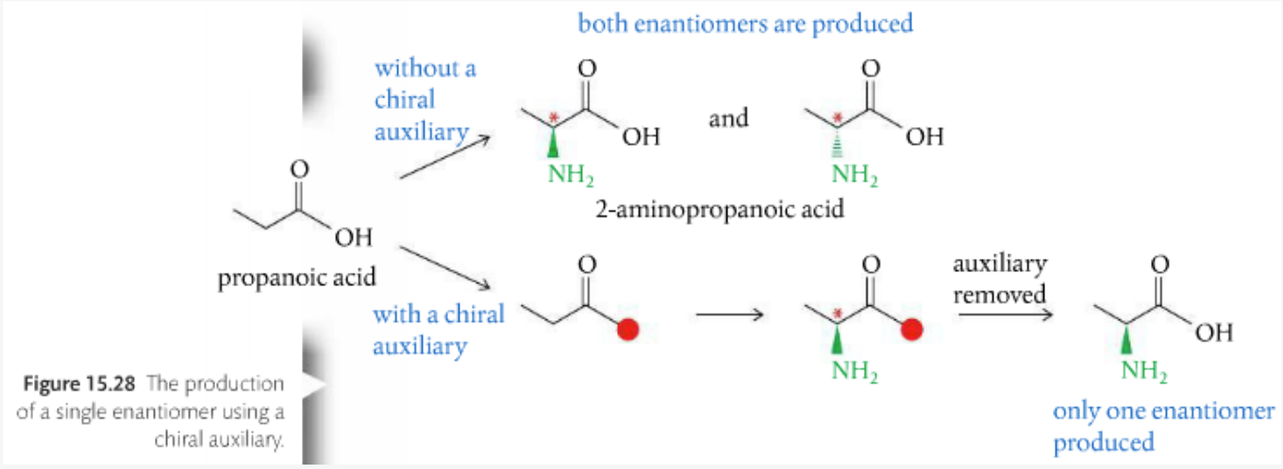


Figure 15.28 The production of a single enantiomer using a chiral auxiliary.

D.7 Taxol: a chiral auxiliary case study

Chiral Auxiliary…

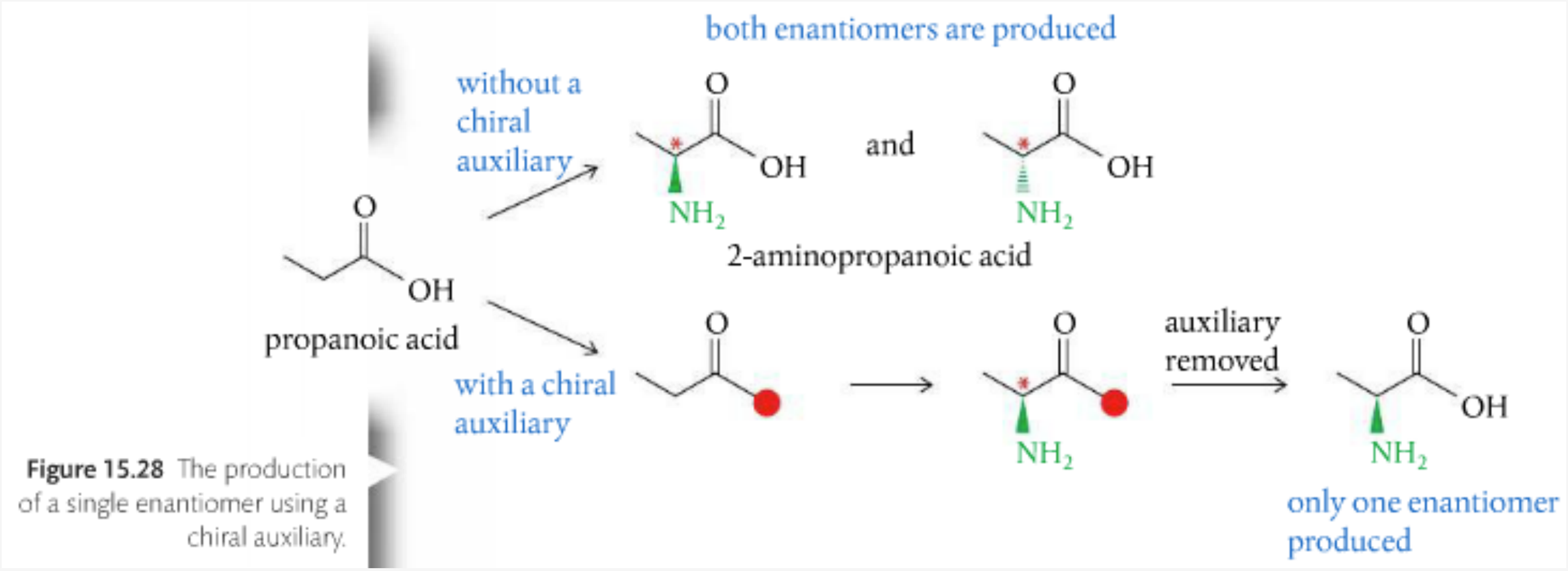


Figure 15.28 The production of a single enantiomer using a chiral auxiliary.

D.7 Taxol: a chiral auxiliary case study

So…

- Taxol - 11 chiral carbons - 30 step process using an auxiliary - poor yield and impractical
- Now…we use the needles and leaves of yew trees - doesn't kill the trees! - more sustainable

- Related compound formed is 10-DAB and then chemically modified into Taxol - a semi-synthetic process
- Conversion requires 13 solvents and a range of other organic reagents - large number of steps and low yield