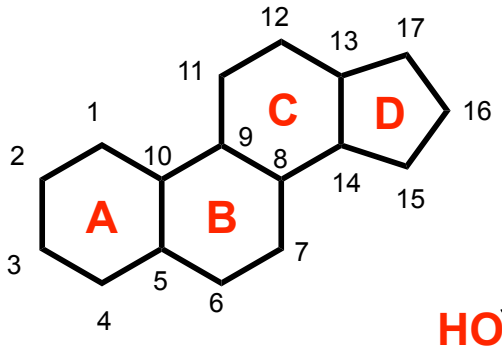
Total Synthesis of Steroids

Krishna P Kaliappan

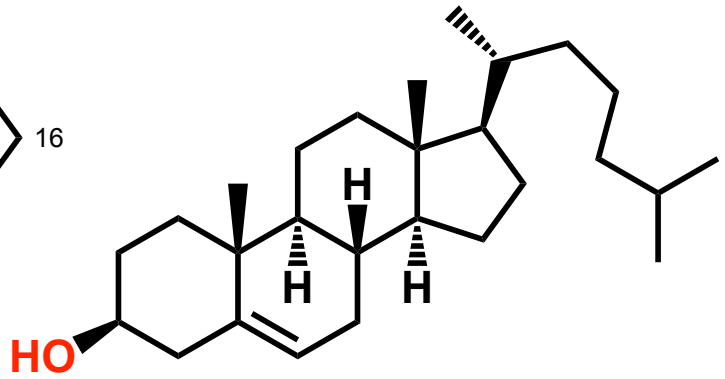
Professor of Chemistry, IIT Bombay

CH-588 Course on Organic Synthesis

Steroids



Numbering of Steroid skeleton



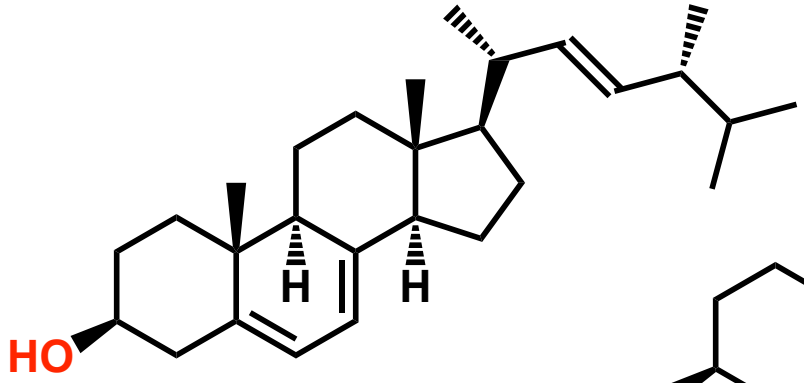
Cholesterol

Steroid skeleton consists of three fused cyclohexane rings and one cyclopentane ring

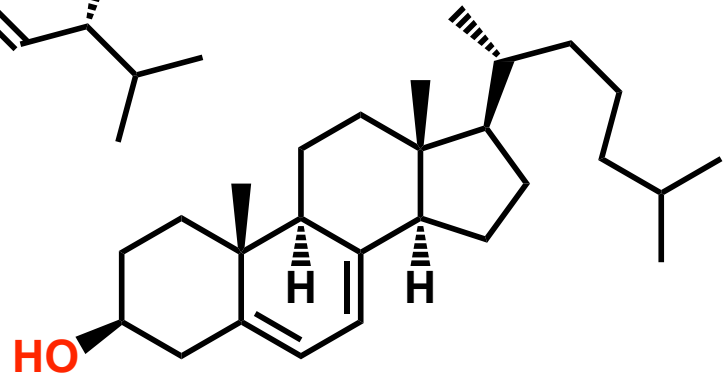
In most cases, there are two angular methyl groups at C-10 and C-13

Substituents on the same side as these two angular methyl groups are β-substituents

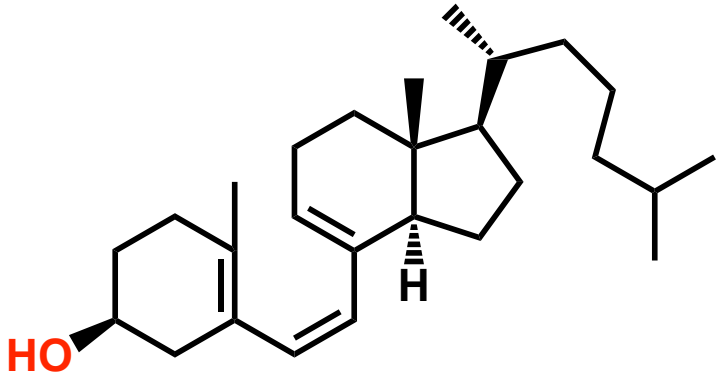
Trans-anti, trans-anti & trans-anti ring junctions



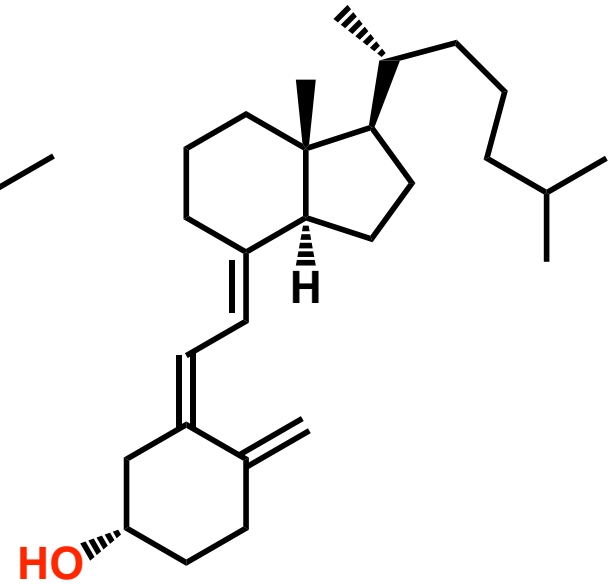
Ergosterol



Dehydrocholesterol

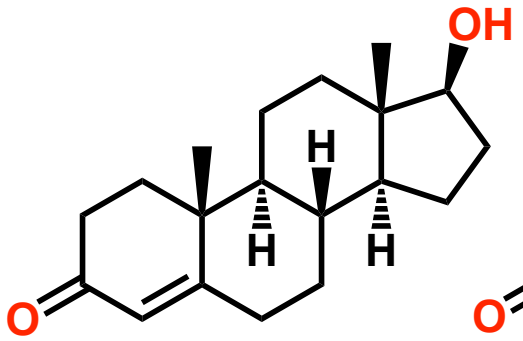


Previtamin D_3

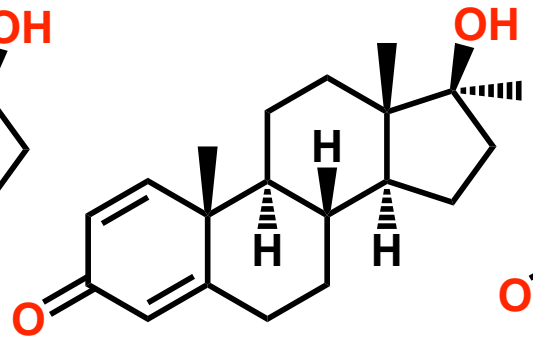


Vitamin D_3

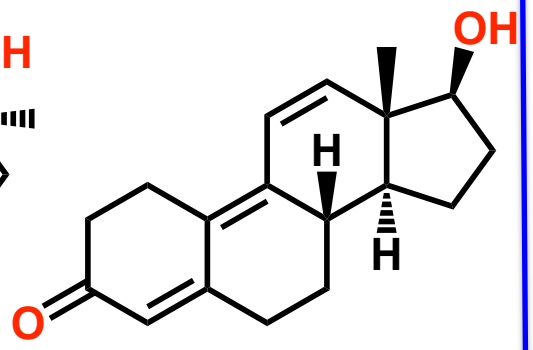
Male and Female Sex Harmones



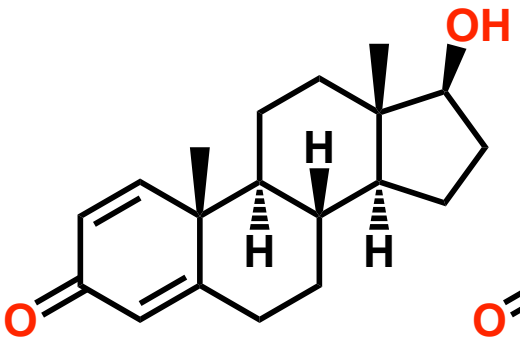
Testosterone



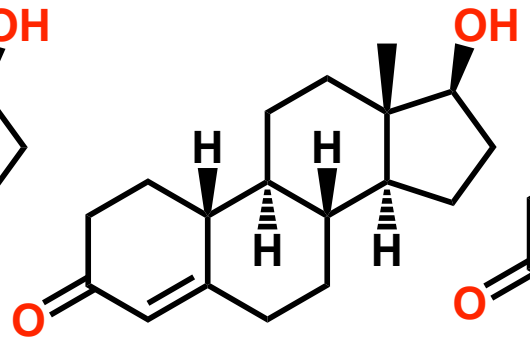
Dianabol



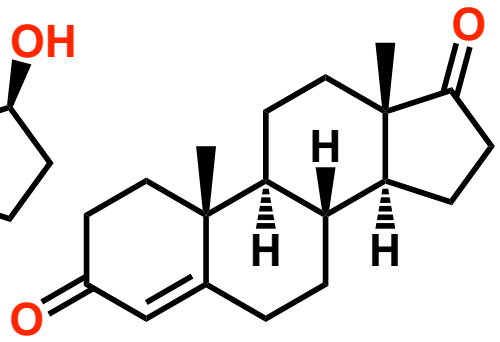
Trendbolone



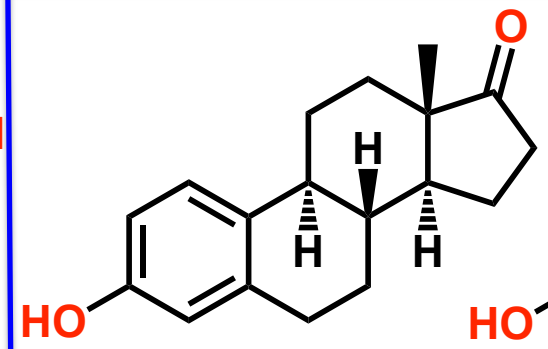
Boldenone



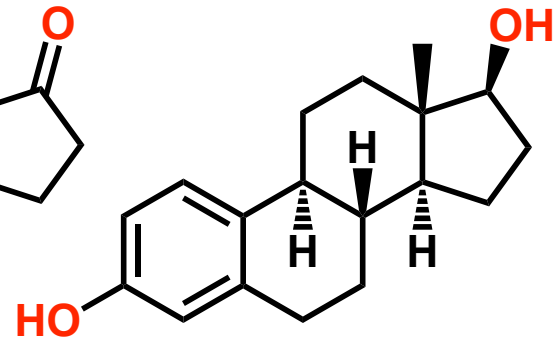
Nandrolone



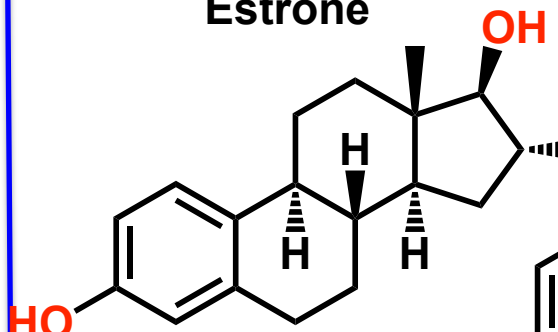
Androstendione



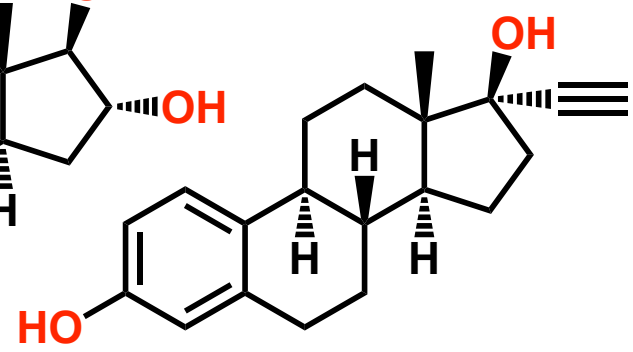
Estrone



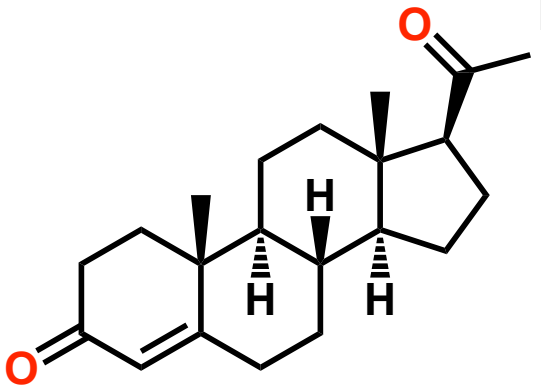
Estradiol



Estriol

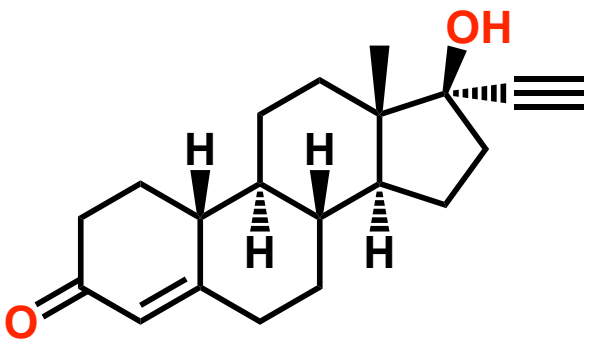


Ethynyl estradiol

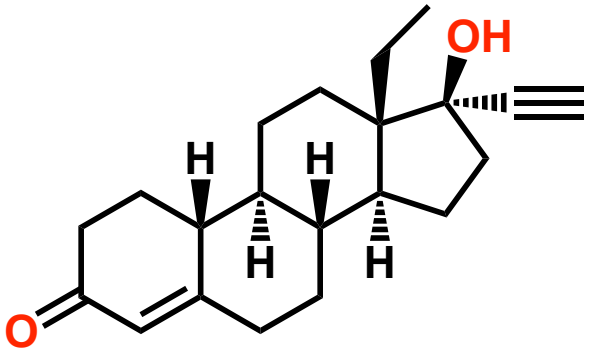


Progesterone

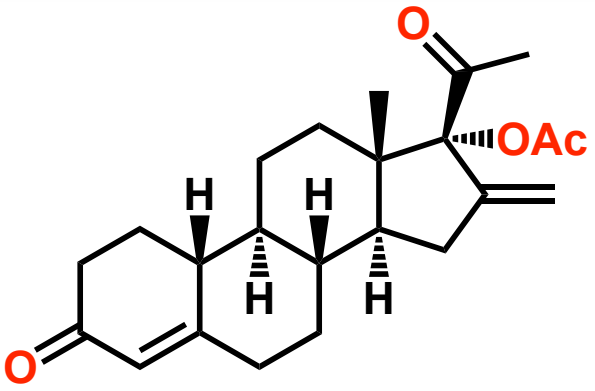
Oral Contraceptives



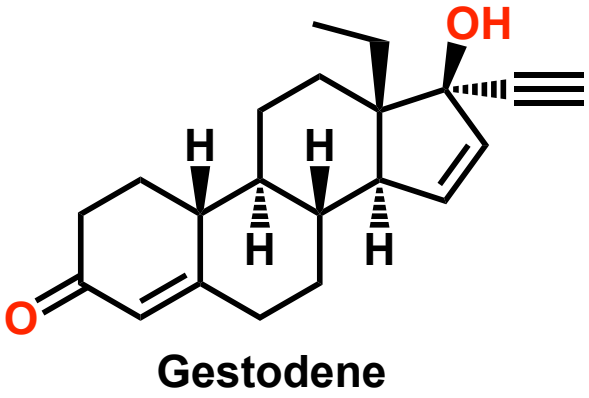
Norethindrone



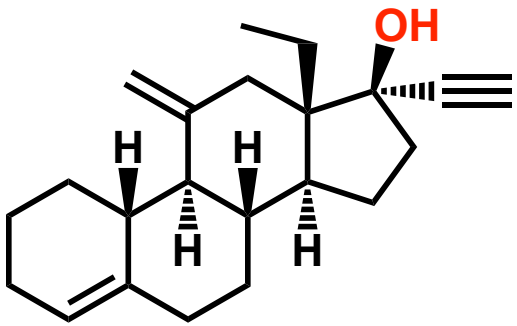
Norgesterol



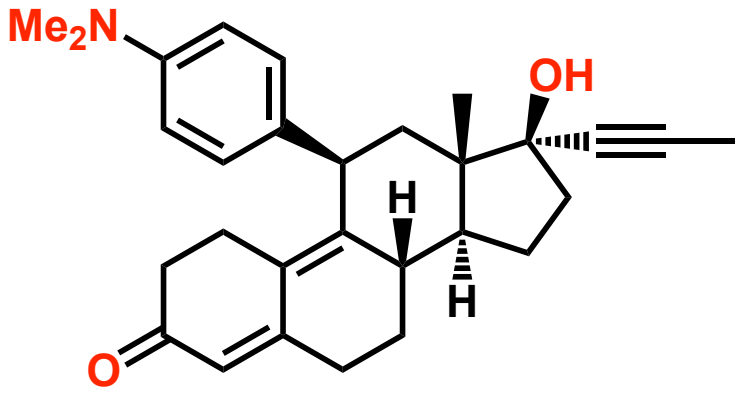
Nesterone



Gestodene

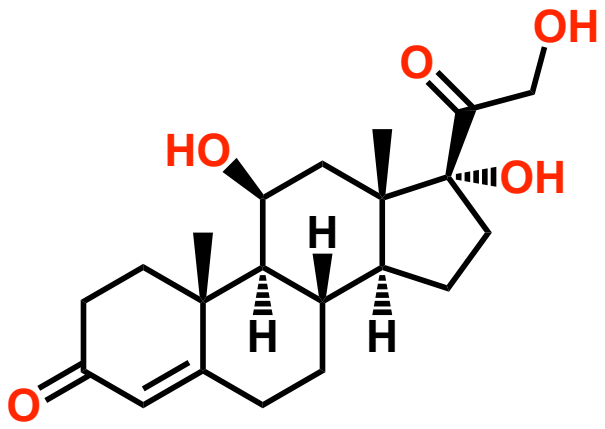


Desogestrel

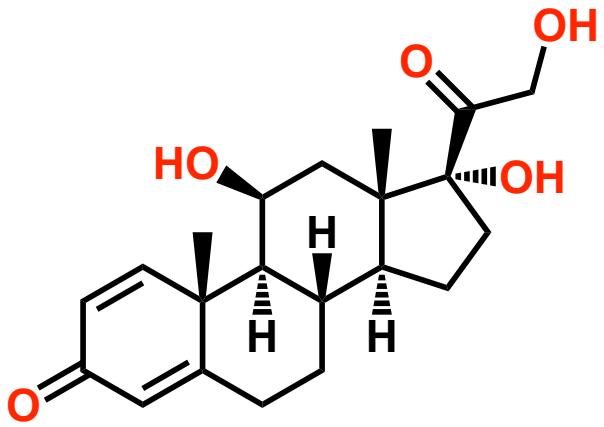


RU-486 (Mifepristone)

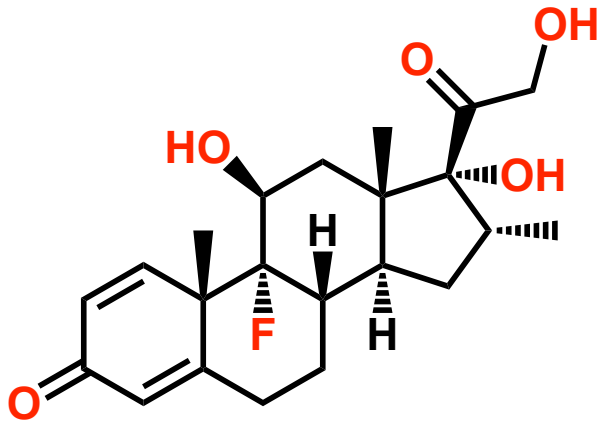
Corticosteroids



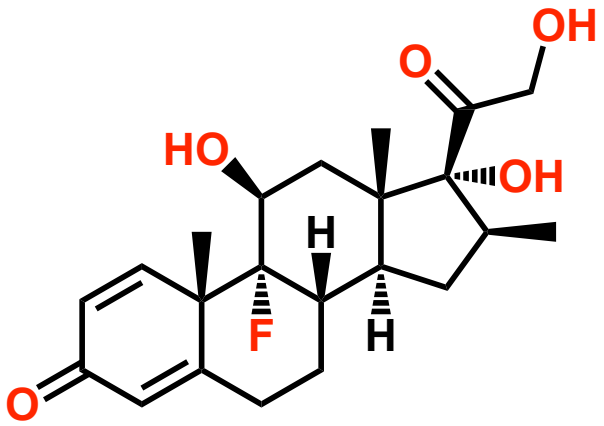
Cortisol



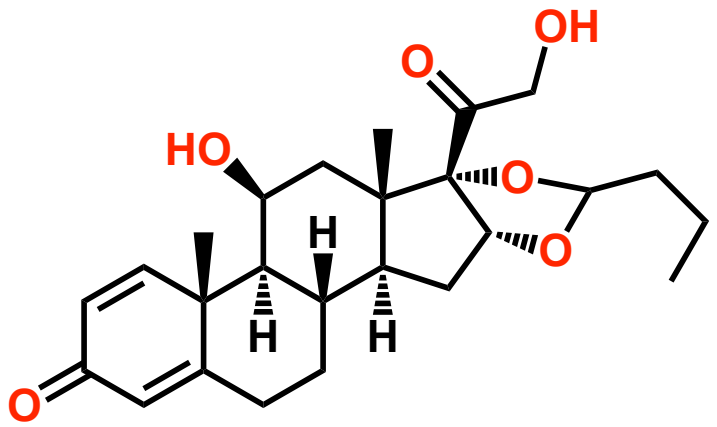
Prednisolone



Dexamethasone

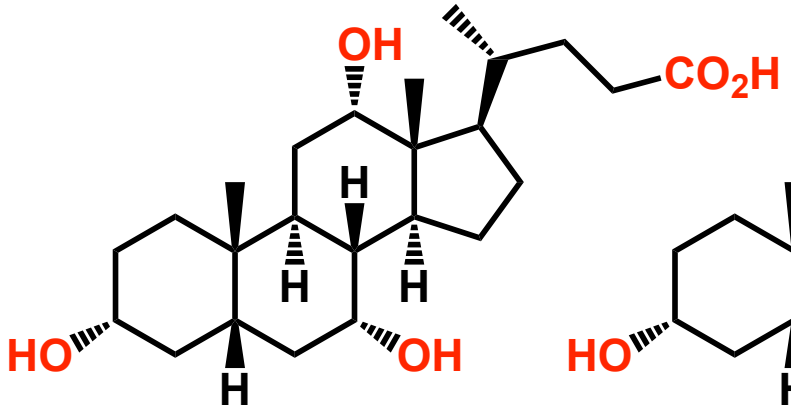


Betamethasone

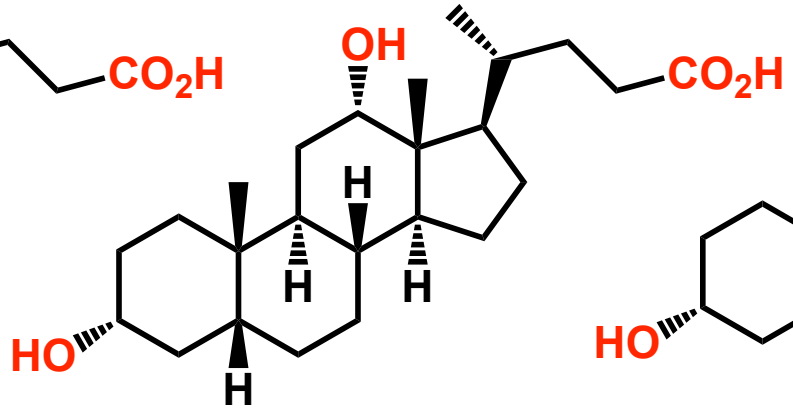


Budesonide

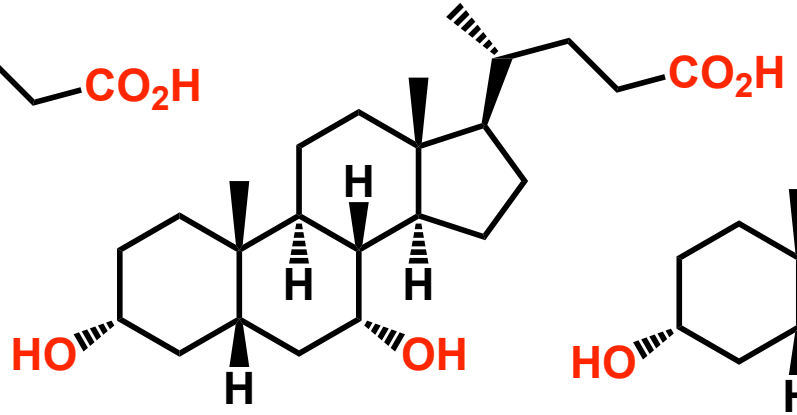
Bile Acids



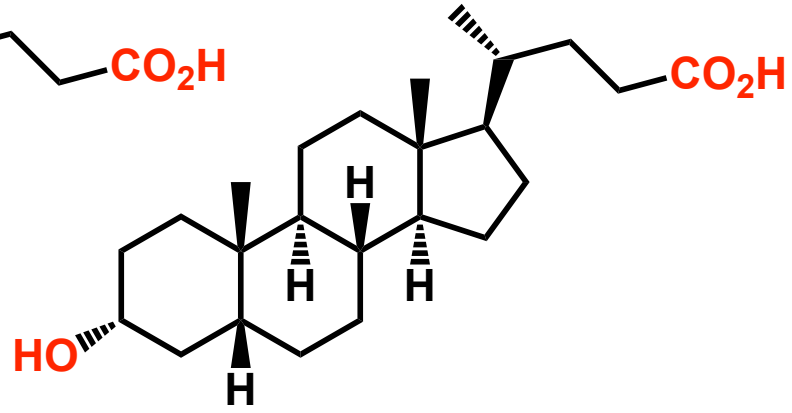
Cholic Acid



Deoxycholic Acid

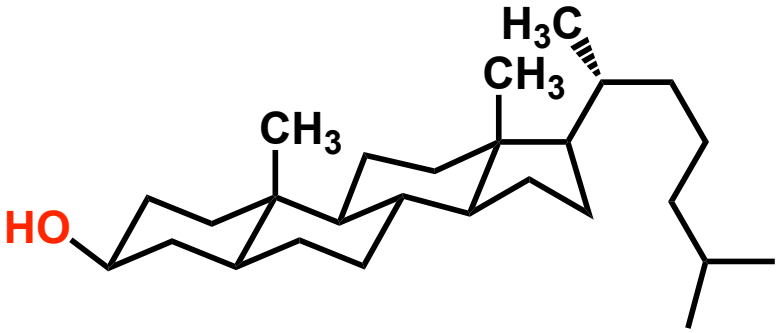


Chenodeoxycholic Acid

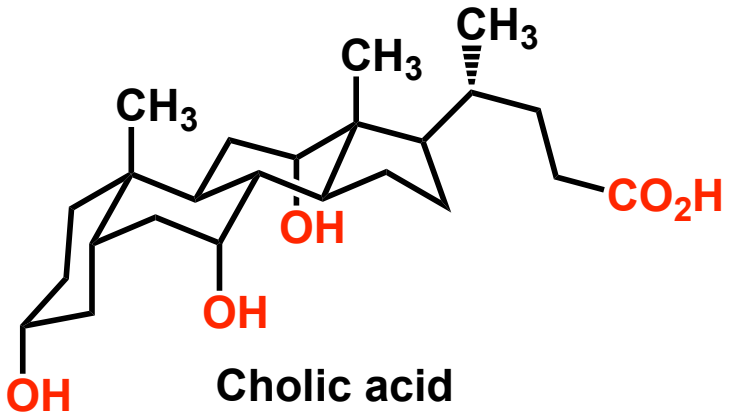


Lithocholic Acid

Conformation

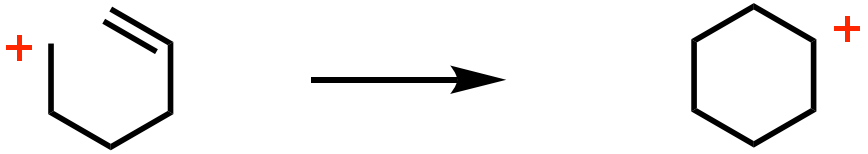


Cholestanol



Cholic acid

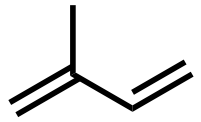
Terpene Biosynthesis



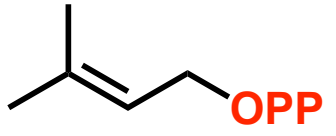
Terpene Biosynthesis

monoterpenes	C10	geraniol
sesquiterpenes	C15	farnesol
diterpenes	C20	geranylgeraniol
steroids	C30	squalene

Isoprene-basic building block

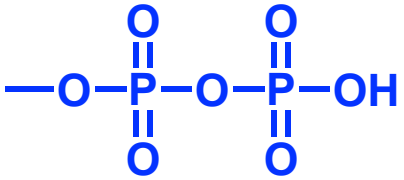


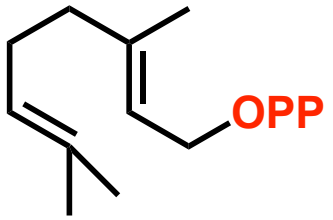
isoprene unit



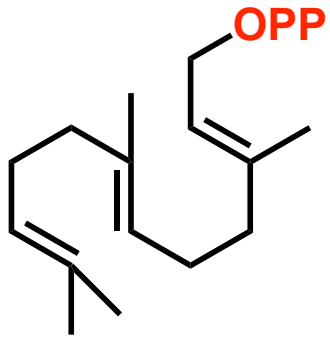
isopentenyl-PP

PP = pyrophospate

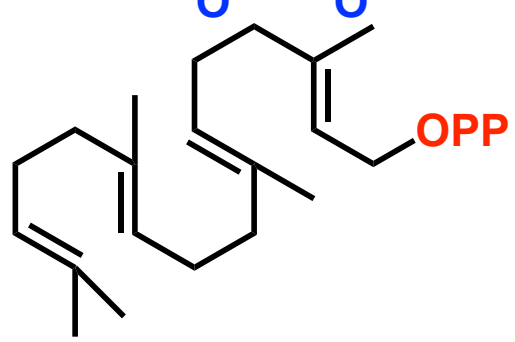




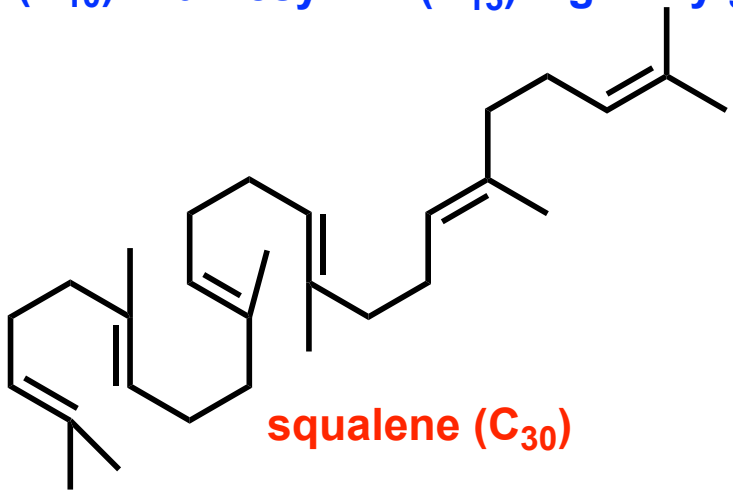
geraniol-PP (C_{10})



farnesyl-PP (C_{15})

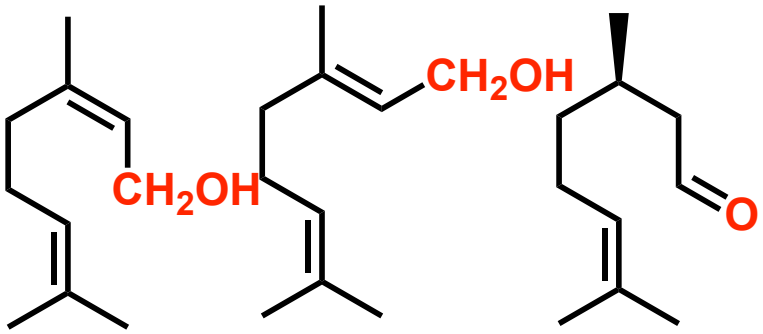


geranylgeraniol-PP (C_{20})



squalene (C_{30})

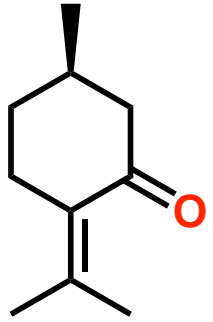
Monoterpenes



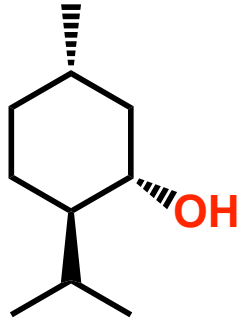
nerol

geraniol

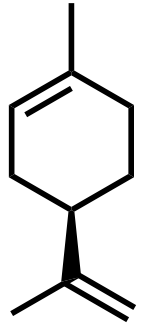
citronellal



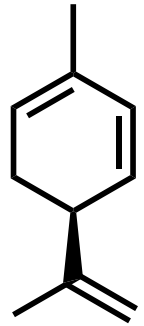
R-Pulegone



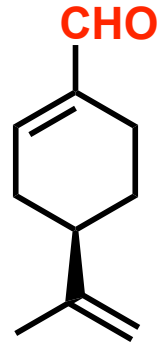
menthol



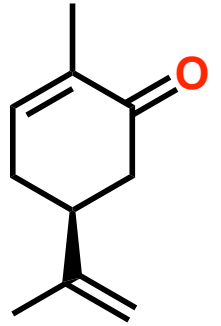
R- limonene



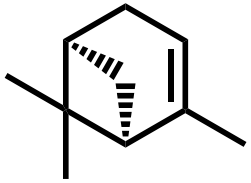
phyllandrene



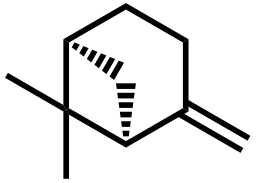
perillaldehye



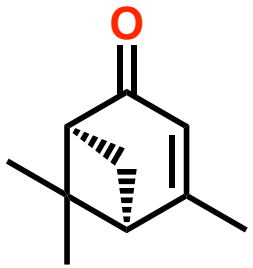
S-carvone



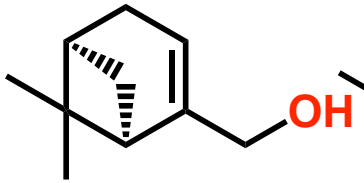
α-pinene



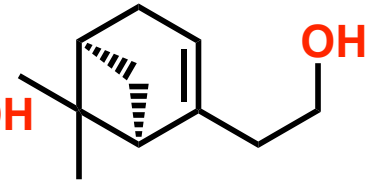
β-pinene



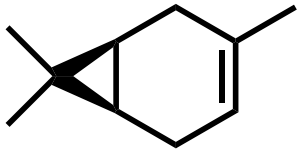
verbenone



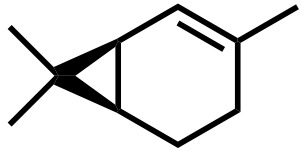
myrtenol



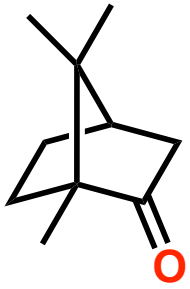
nopol



3-carene

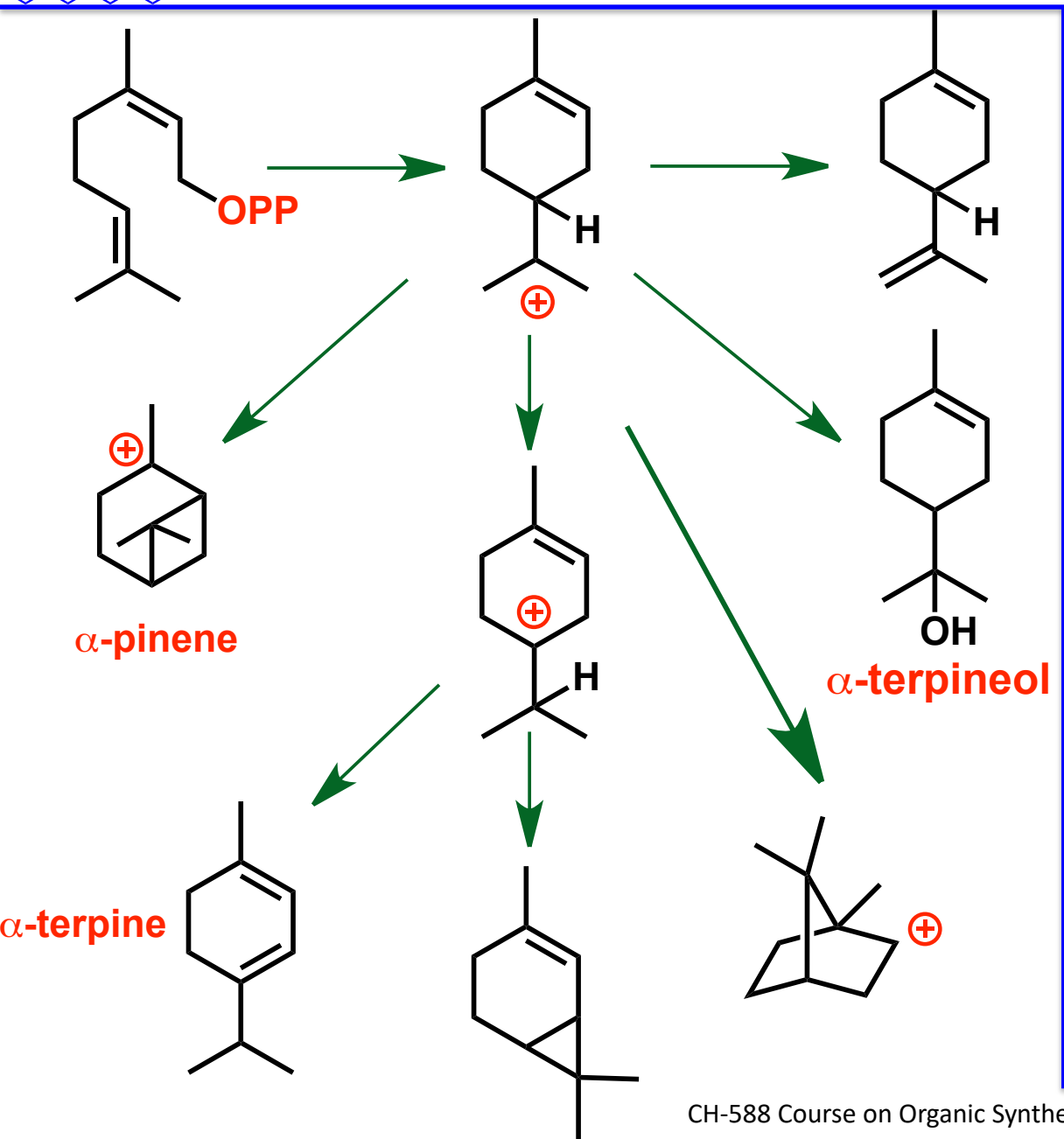


2-carene

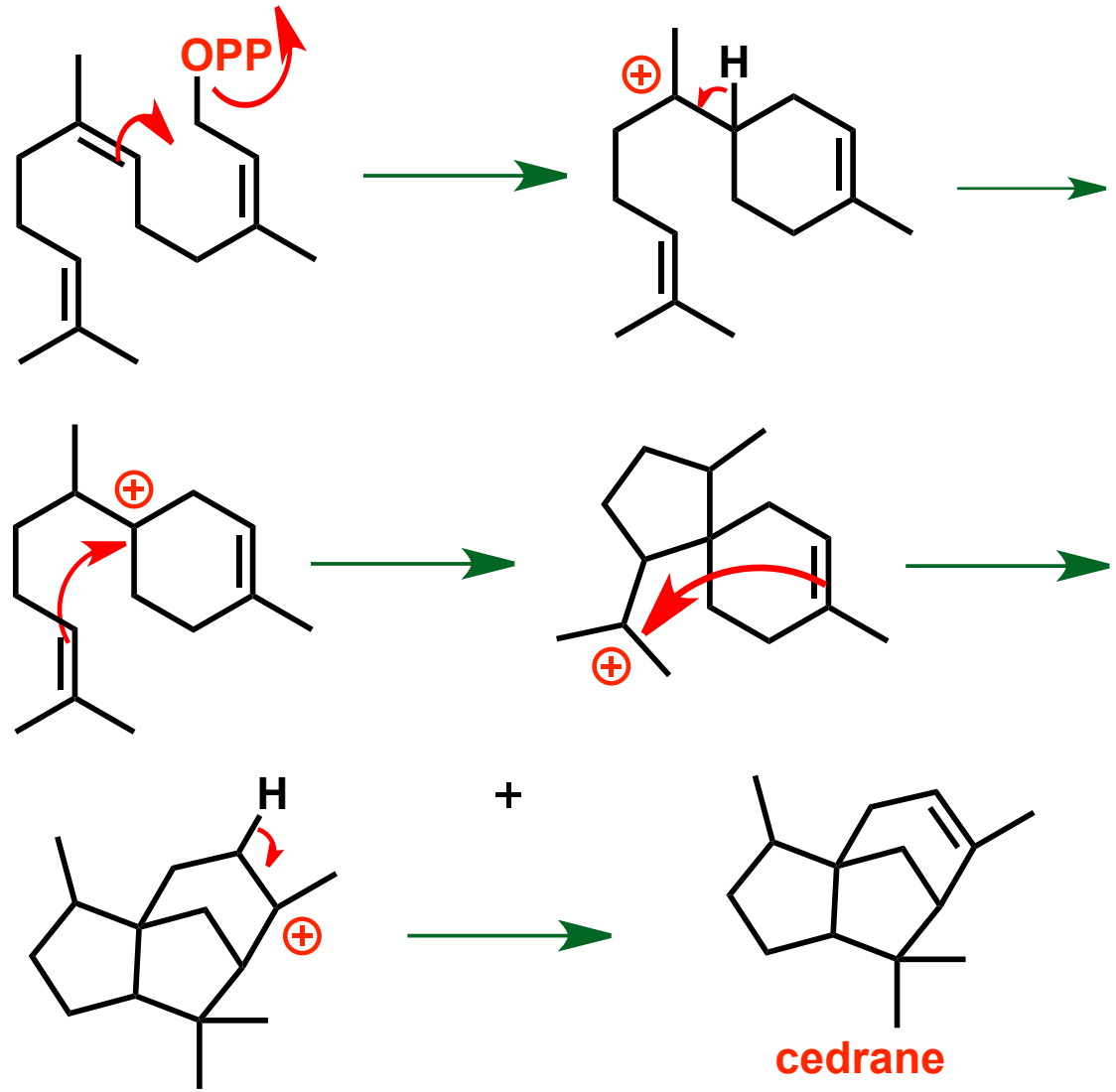


camphor

Terpene Biosynthesis



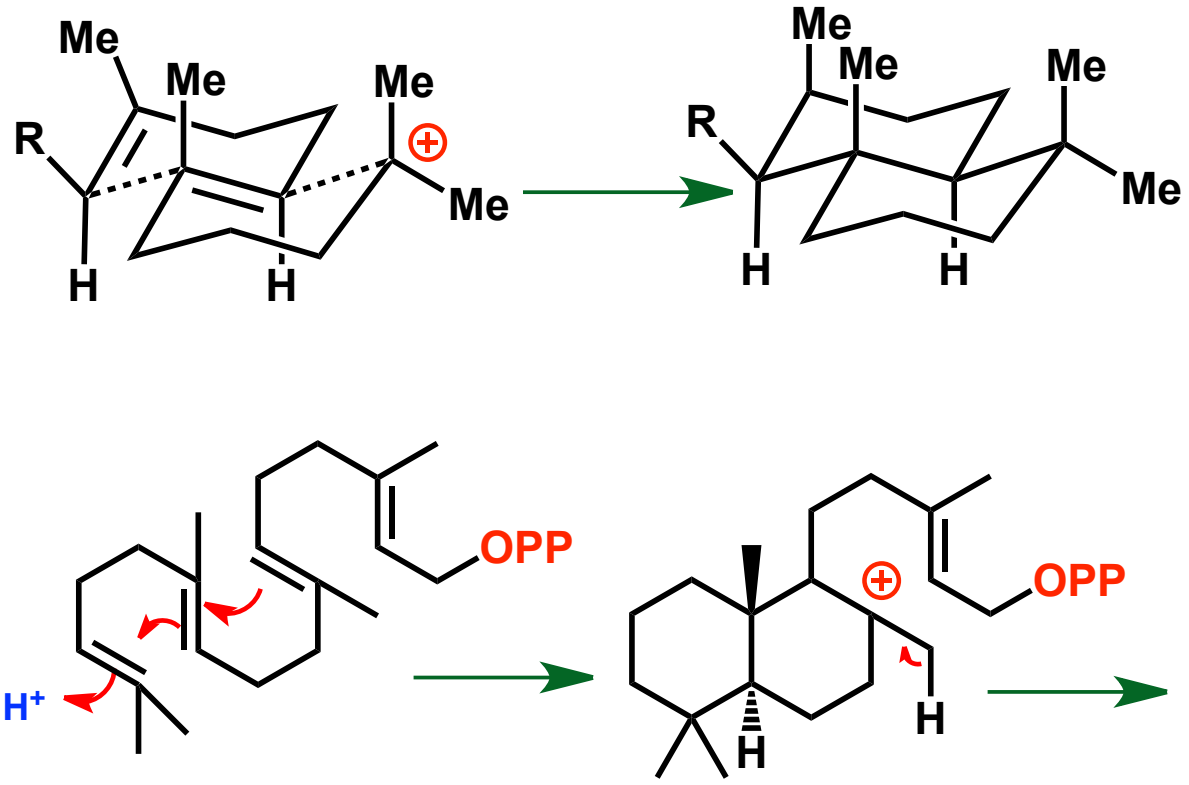
Biosynthesis of cedrane



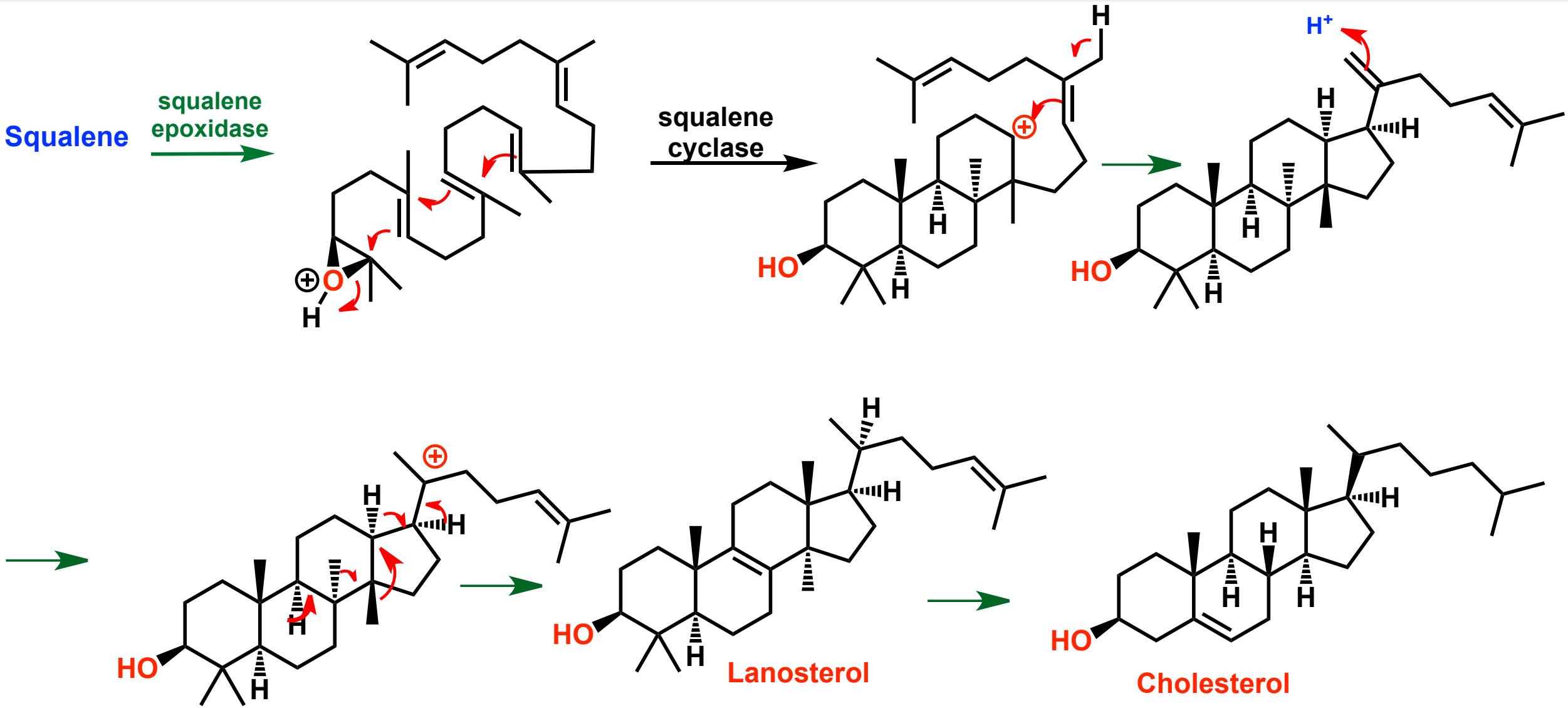
Terpene Biosynthesis

Stork-Eschenmoser Hypothesis - olefin geometry is preserved in the cyclization reaction

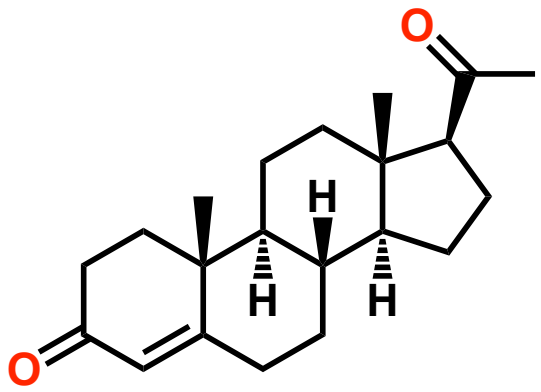
trans olefin leads to *trans* fused ring junction



Steroid Biosynthesis



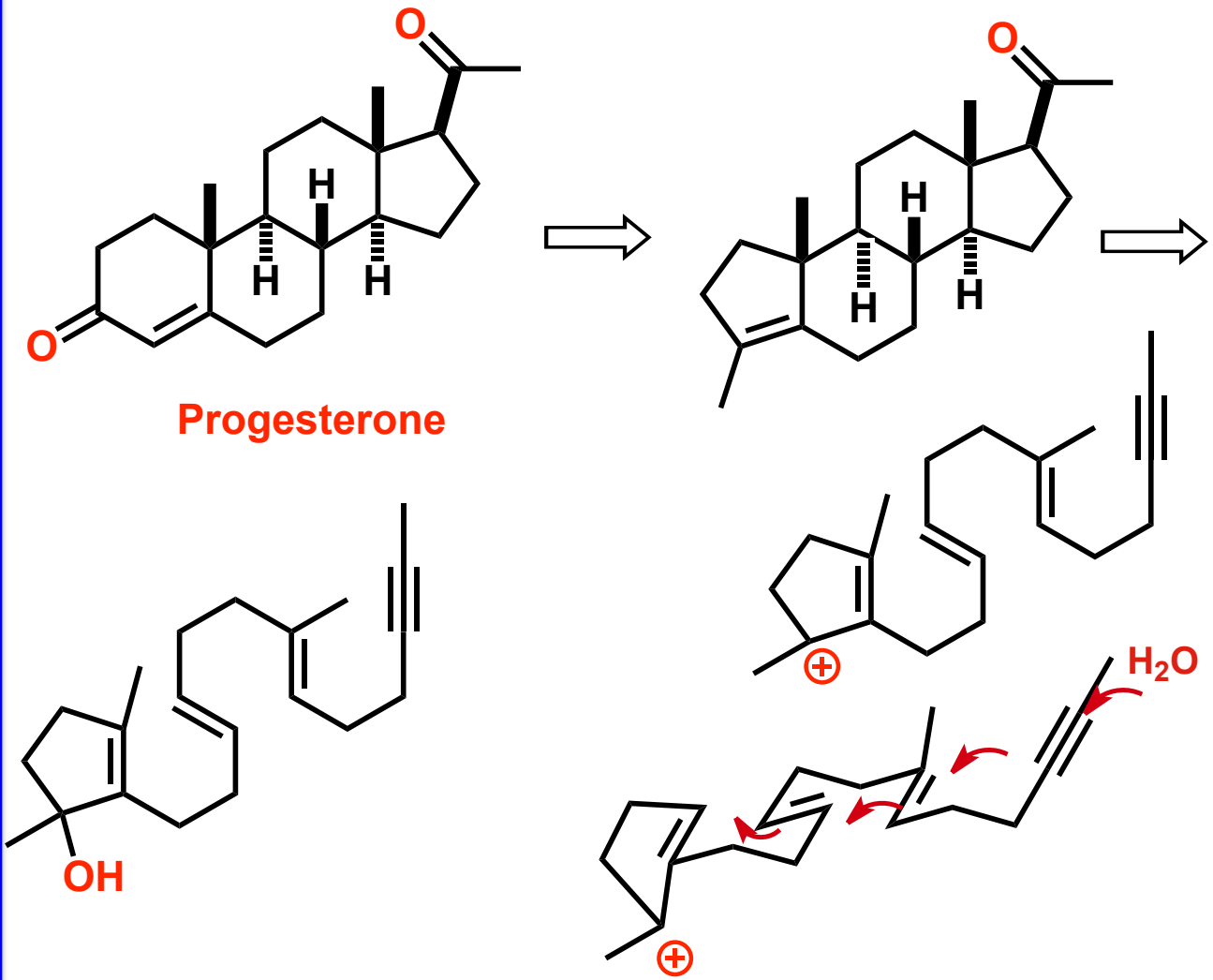
Progesterone



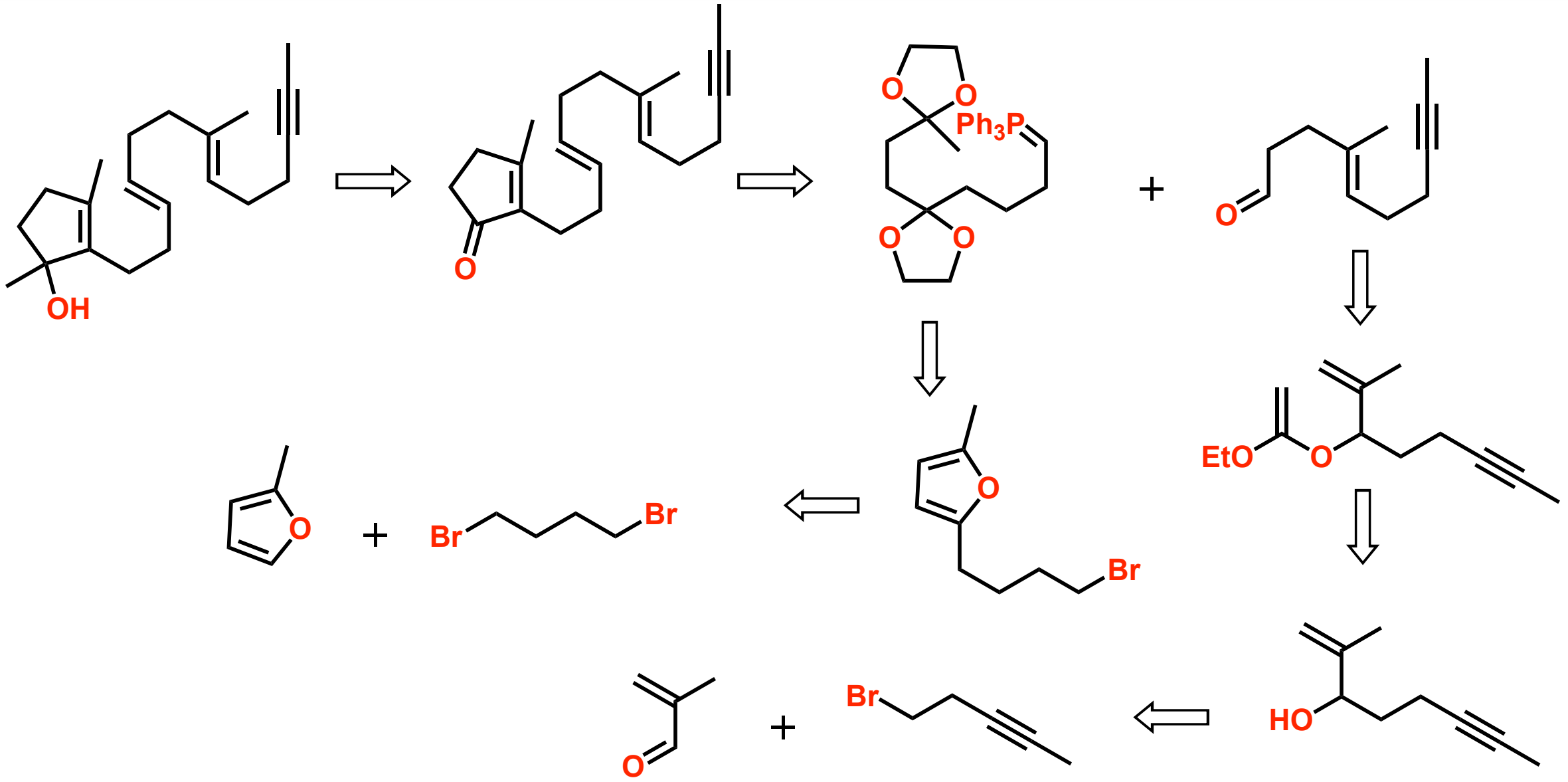
Progesterone

- There are several synthetic approaches known for this steroid
- An interesting approach was developed by W. S. Johnson at Standford University based on Stork-Eschenmoser's hypothesis of biomimetic polyolefinic cyclizations

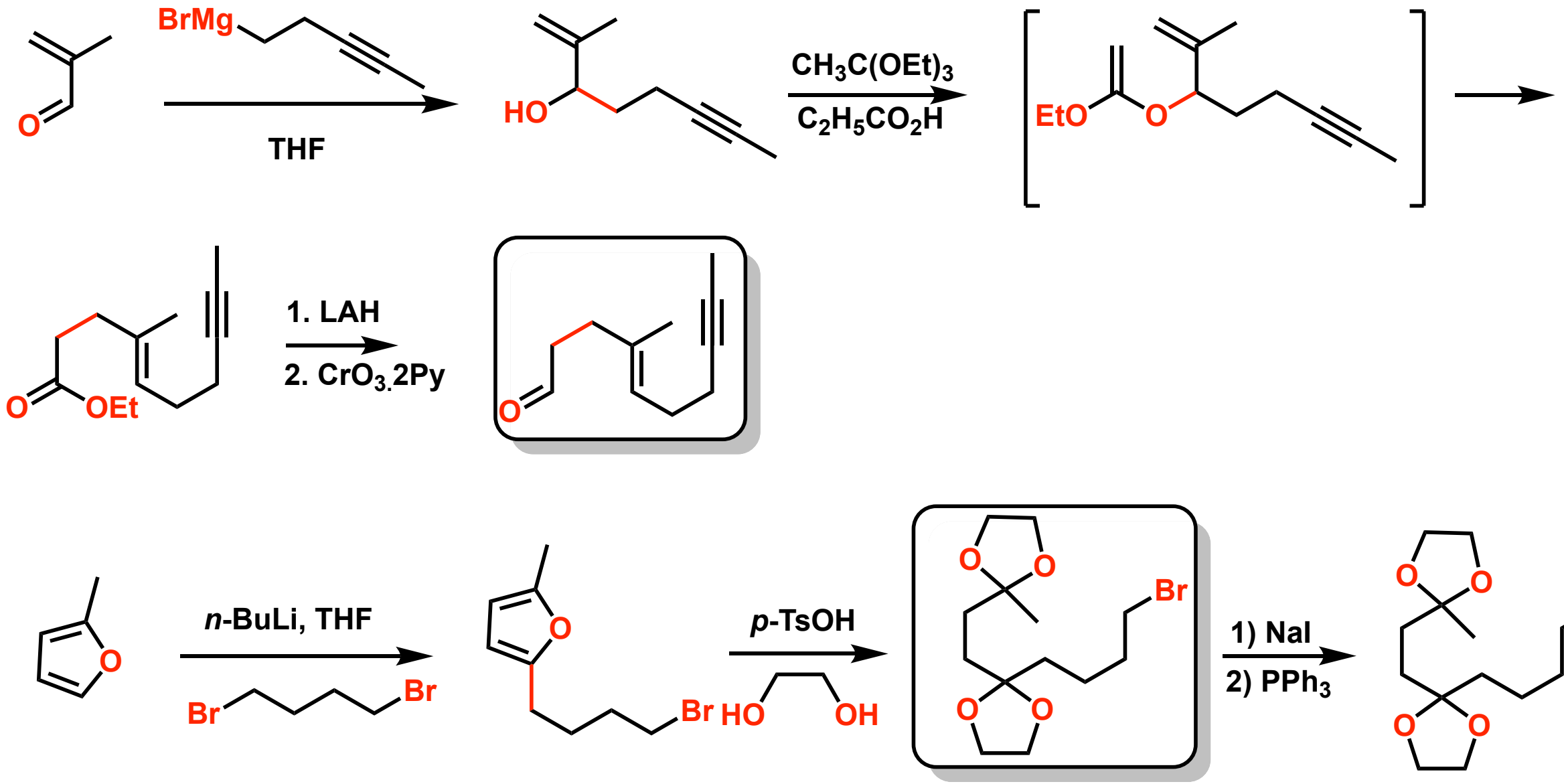
Retrosynthesis



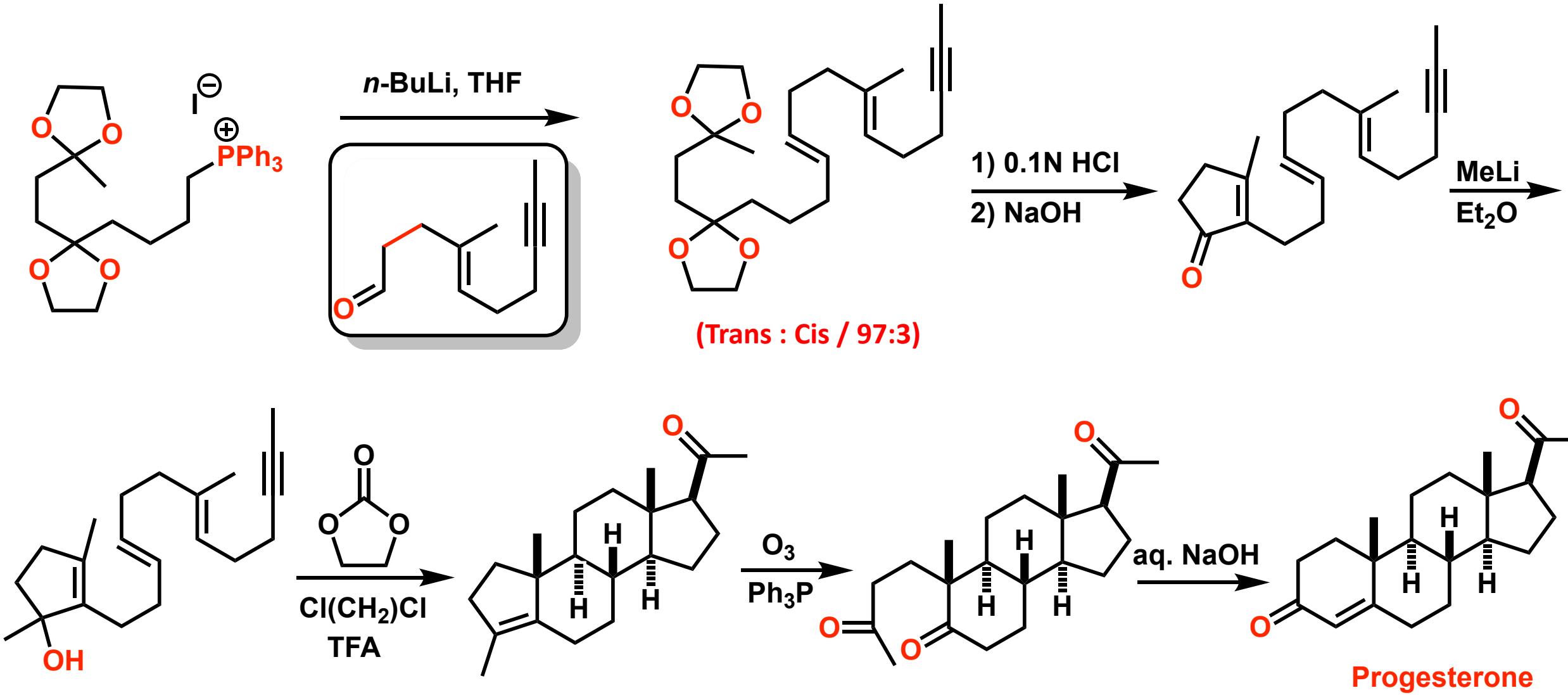
Progesterone



Total Synthesis of Progesterone



Total Synthesis of Progesterone



Johnson, W.S. *et al*. ***J.Am. Chem. Soc.*, 1971**, *93*, 4332.