Total Synthesis of Progesterone

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Importance of Progesterone

• Progesterone is a natural steroid vital for a variety of functions in the human body
  ➢ Pregnancy
  ➢ Menstrual cycle
  ➢ Embryogenesis
  ➢ Metabolic intermediate

• Used as a medication
  ➢ Used to reduce the risk of uterine of cervical cancer
History of Progesterone

1929 - the hormonal action of progesterone was discovered

1934 - pure crystalline progesterone was obtained and the chemical structure was known

1934 - synthesized from stigmasterol and pregnanediol

![Chemical structures of stigmasterol, pregnanediol, and progesterone](image_url)

Adolf Friedrich Johann Butenandt
German Biochemist
1939 Nobel Prize in Chemistry
Total Synthesis of Progesterone

• William S. Johnson at Stanford University published his total synthesis of progesterone in 1971

• This total synthesis required 15 steps


Retrosynthetic Pathway for Progesterone


Retrosynthetic Pathway for Progesterone


Under conditions that would facilitate the heterolytic cleavage of the C-OH bond, it is conceivable that the tertiary allylic carbonium ion would participate in a polyolefinic cyclization. In one step, three rings and six contiguous stereogenic centers can be created.
Retrosynthetic Pathway for Progesterone


Under basic conditions, the deprotonation of Hₐ can form an enolate. This enolate would be in close proximity to an electrophilic carbonyl which could undergo an intramolecular aldol condensation. The subsequent dehydration can produce the desired product.

Retrosynthetic Pathway for Progesterone


The Wittig product of a non-stabilized ylide with an aldehyde would be expected to afford an olefin with Z geometry. The Schlosser modification allows for the E olefin to be the major product.


Retrosynthetic Pathway for Component 1


Retroynthetic Pathway for Component 1

The action of ethylene glycol on a substituted furan could, in the presence of an acid catalyst, result in the formation of the diacetyl.


Retrosynthetic Pathway for Component 2

Johnson-Claisen rearrangement is utilized for the stereo-controlled construction of the trans tri-substituted double bond.

Retrosynthetic Pathway for Component 2

Total Synthesis of Progesterone

- This 15-step synthesis can be broken down into three major components

Synthesis of Component 1


Synthesis of Component 1


Hydroquinone is present to suppress the formation of polymeric material.
Synthesis of Component 1

NaCl, NaBr aren’t soluble in acetone while NaI is. From here the phosphonium iodide was crystallized from acetone as colorless microcrystals.

Synthesis of Component 1


Component 1 is now complete
Synthesis of Component 2


Synthesis of Component 2


Synthesis of Component 2

Synthesis of Component 2


Synthesis of Progesterone


Synthesis of Progesterone


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Trifluoroacetic acid (TFA) induces a heterolytic cleavage of the C-O bond to afford the tertiary allylic cation.

Ethylene carbonate traps the vinyl cation and undergoes conversion to the methyl ketone during workup.
Synthesis of Progesterone


Synthesis of Progesterone


Conclusion

The paper states that the yields hadn’t been optimized. Starting from the Wittig reaction the yield is 13%.

Total of 15 steps

This total synthesis highlights a Wittig reaction with the Schlosser modification, a Johnson Orthoester Claisen Rearrangement, the Finkelstein reaction, an oxidation using Collin’s reagent and a polyolefinic cyclization.

Thank you for your attention!

Questions?
Synthesis of Component 2

Synthesis of Component 2

Synthesis of Component 2


Synthesis of Component 2

Synthesis of Component 2


Synthesis of Component 2


Synthesis of Component 2
