An Ecofriendly Microwave Assisted Synthesis of 1, 5-Di-Oxo-4(2'-Carboxehtyl)-7a-Methyl Tetrahydro Indane, Akey Intermediate of Steroids

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Abstract- *In the present innovative study a convenient microwave assisted synthesis of 1,5-di-oxo-4(2'-carboxehtyl)-7a-methyl tetrahydro indane - a key intermediate of steroids has been carried out by using (S)-proline as catalyst. The highlights of the present protocol are,greater overall yield during the synthesis (92%) and it is achieved via usingecofriendly protocol by using cheap and commercially available chemicals.*

Keywords- Microwave assisted synthesis, Terpenoids, Steroids.

I. INTRODUCTION

Synthesis of significant and desired enantiomer is of great importance in the pharmaceutical world due to its medical applications. As we knowsteroids are the most important components of human anatomy and hence various research groups are attracted towards synthesis of the same[1].

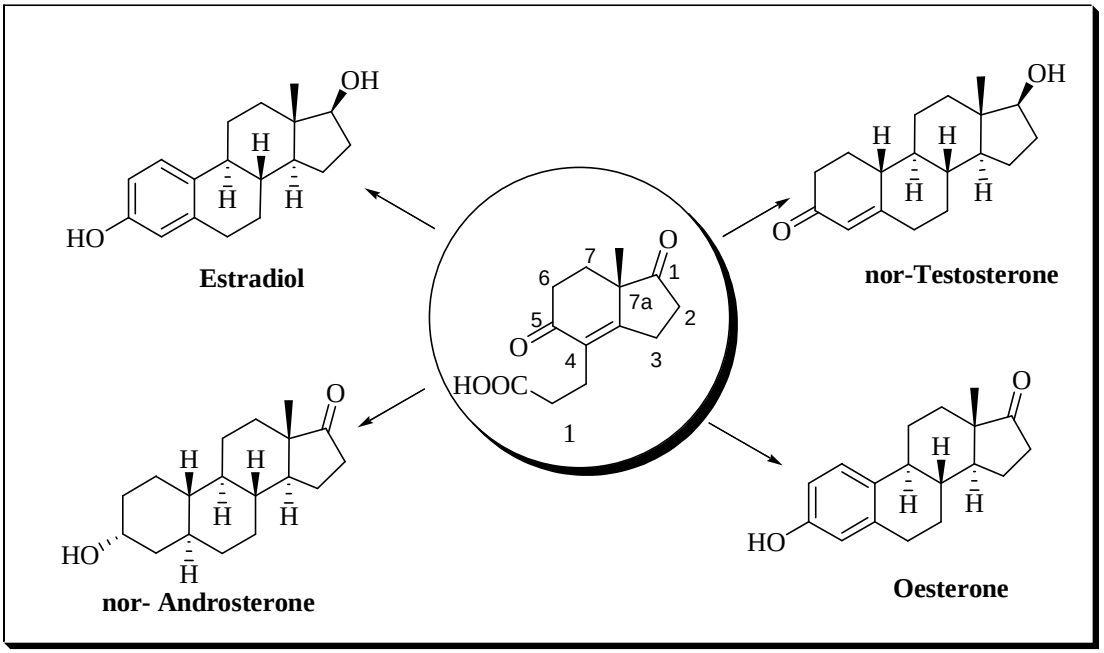


Figure 1

From literature survey it is clear that over the last few years,several synthetic approaches for both steroids and vitamin Dlike structures have emerged in the area of steroid chemistry[1]. Most of these approaches have been drafted in a sequential manner, such as the construction of the aliphatic side chain,annulations of the *trans*-hydroindane **C-D** ring, its elaboration through **B**-ring closure,followed by intra-molecular cyclo-additions or transition metal catalysed reactionsand finally, synthesis ofring **A.**[1] Among these steps construction of the **C-D** ring is the most significant and key step, since axial methyl group as well as ring junction differentiate the one molecule from other[1] (Figure 1).

Hence annulations of C-D ring intermediate has dragged attention of variousresearch groups and various protocols have been reported for the synthesis of the same[1,2,3].In summaryintermediate compound (7aS)-1-5-dioxo-4-(2'-carboxyethyl)-7a-methyl tetrahydro-indane (**1)**or it's

corresponding hydroxyl derivative (**2**)are the significant key intermediate of various steroids[1]**(Figure 2).**

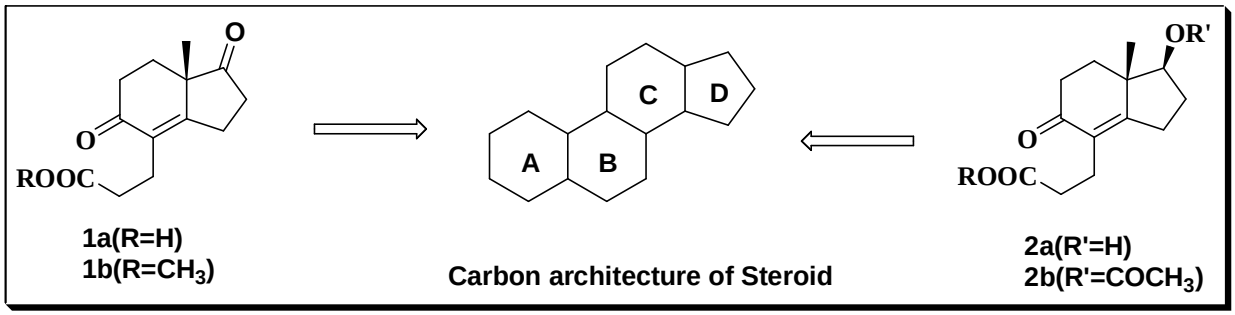
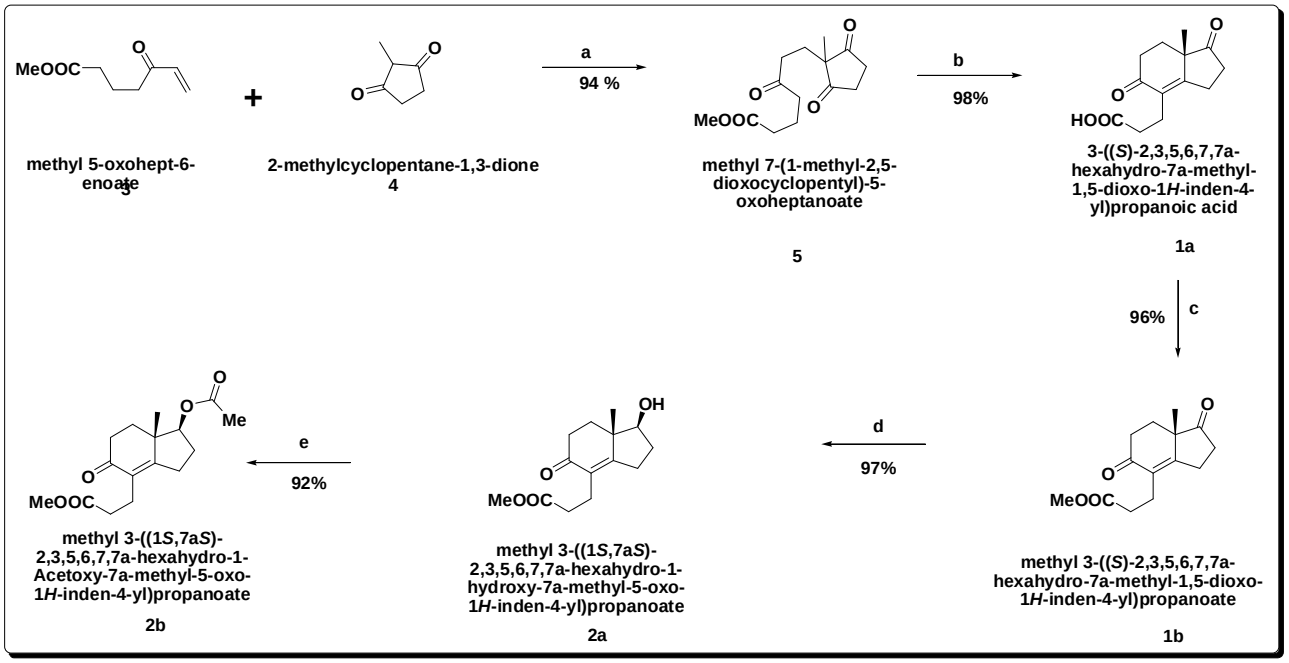


Figure-2

Different approaches are utilized for the synthesis of this optically active **C-D** ring system as below[1]:

1) Chemical resolution of diastereomers by recrystallization of respective salts or by chromatographic separation of diastereomers.
2) Desymmetrization of 2-substituted-1, 3-cyclopentanediones (**D** ring) either by a microbial reduction, or by formation of diastereoisomers, or by stereoselective reduction.[1]
3) By amino acid ctalysed asymmetric Robinson annulation under Hajos–Parrish–Eder–Sauer–Wiechert reaction conditions.[2]
4) Use of chiral auxiliaries, as chiral metal–ligand complexes or chiral bases.[1, 3]
5) Chiral pool approach via utilisation of the naturally available substrates as starting material like quinic acid, malic acid, diethyl tartrate, mannitol, xylose, arabinose, glucose and camphor derivatives.[1]

But all of the above reported protocols are comprised of either lengthy reaction sequence or longer reaction time with low overall yields &with variable optical purity of the product. Further, above methodinclude use of carcinogenic solvents and narcotic drugs. Whereas, ecofriendlyprotocolsas microwave assisted synthesis via Robinson annulationsare not yet explored.Owing to the significance of intermediate(7a*S*)-1-5-di-oxo-4-(2`-carboxyehtyl)-7a-methyl tetrahydro-indane (**1**)and in continuation with earlier our research work over*S* (+)Proline catalyzed asymmetric cyclisation we planned to synthesizethe same intermediate(**1**). After synthesis further the structure ofintermediate (1) is confirmed via functional group transformation to (1*S*,7a*S*)-1-acetoxyoxy-5-oxo-4-(2`-carbomethoxyehtyl)-7a-methyl tetrahydro-indane followed by X-ray cryatallographyllic characterization.**(Figure 2)**[4, 5]



Scheme 1

Scheme1. *Reagents and conditions:* (a) TEA/(S)Proline/Toluene, reflux; (b) Benzene/(S)Proline/H^+,

reflux; (c) MeOH / H^+, reflux; (d) $NaBH_4$ / MeOH; (e) Ac_2O, Et_3N, DCM.

As shown above in the **scheme-1**, Michael addition of methyl-5-oxo-6-heptenoate (**3**) with 2-methylcyclopenten-1,3-dione (**4)** gave methyl ester of 7-(1-methyl-2,5-dioxo-cyclopentyl)-5-oxo-heptanoic acid (**5**), which on further annulations yielded (7a***S***)1,5-dioxo-4-(2'-carboxyehtyl)-7a-methyl tetrahydro indane (**1a**). The esterification of the compound (**1a**) has been carried out via reflux with MeOH/H^+ to yield (7a***S***)1,5-dioxo-4-(2'-carbomethoxyehtyl)-7a-methyl tetrahydro indane (**1b**). Reduction 1, 5-dioxo-4-(2'-carbomethoxyehtyl)-7a-methyl tetrahydro indane (**1b**) with $NaBH_4$ gave 1-hydroxy-5-oxo-4-(2'-carbomethoxyehtyl)-7a-methyl tetrahydro indane (**2a**) and it is subjected for acylation to yield 1-acetoxy-5-oxo-4-(2'-carbomethoxyehtyl)-7a-methyl tetrahydro indane (**2b**). Formation of opticallypure1-acetoxy-5-oxo-4-(2'-carbomethoxyehtyl)-7a-methyl tetrahydro indane (**2b**) compound is confirmed by X-ray crystallography (Scheme 1).

II. CONCLUSION

In conclusion, we have established the asymmetric enantio selective synthesis of (7a***S***)-1, 5-dioxo-4-(2'-carboxyehtyl)-7a-methyl tetrahydro indane (**3a**) in>95% e.e. via using s(+)proline as catalyst.

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