Abstract

Chapter I: A general introduction to steroids and pentacyclic triterpenoids

Natural products such as steroids, terpenoids, alkaloids, flavonoids play a major role in drug discovery, and nearly half of all newly introduced drugs into the market in the past two decades are natural products or their direct derivatives. Steroids are able to penetrate cells and bind to nuclear and membrane receptors. To perform some of the fundamental biological functions, the steroid system is naturally selected and this is not only the basis of new discoveries in this field but is also the source of interests of biochemists and endocrinologists. Sterols, oxysterols, secosteroids, bile acids, hormones and saponins are some of the important steroids.

On the other hand, pentacyclic triterpenoids (PTs), the secondary metabolites, are widely distributed in plants and are traditionally used as medicines. A number of natural PTs are potent and unique biologically active molecules. In order to exploit the therapeutic potential of natural PTs and/ or their derivatives, intense pharmacological and mechanistic studies have been carried out. Anti-HIV, Antitumor, antiviral, anti-inflammatory, antidiabetic, antiparasitic, antimicrobial, cardio-hepato- and gastro-protective, analgesic and wound-healing effects are included in these bioactivities. Several PTs are now being marketed as therapeutic agents, and a couple of natural/ synthetic PT derivatives are now under clinical trials. Friedelane, lupane, ursane, oleanane, serratane are some of the important groups of the PT series.

Thus, in this chapter, a general description of the steroid and PT groups of natural products, giving emphasis on their fundamental skeletons, classifications etc. along with their immense importance are covered in brief.

Chapter II: Transformative reactions of steroids using mercuric(II) acetate and *N*-bromosuccinimide

Section A: Action of mercuric(II) acetate on 16-Dehydropregnenolone acetate (16-DPA)

The versatile oxidizing capacity of mercuric acetate led the investigation of its action on 16-dehydropregnenolone acetate (16-DPA), an important steroid moiety. When 16-DPA was treated with mercuric(II) acetate, a cyclic ether derivative was formed. The cyclic ether was actually introduced onto the ring-D of 16-DPA, involving the carbonyl oxygen and the double bond in its α,β-position. Hence, a single-step conversion of exocyclic α,β-conjugated

ketone functionality of a steroid resulted a ring-D-fused four-membered cyclic ether which preserves the main significance of the study.

Section B: Action of *N*-bromosuccinimide (NBS) on cholesterol and β-sitosterol: synthesis of A-ring aromatized steroids in solid phase

A thorough review consequences the importance given towards the selective aromatization of steroids and thus working on the subject produced finally a novel synthesis of A-ring aromatized cholesterol and β-sitosterol *via* a very simple one-pot solid phase reaction using *N*-bromossuccinimide (NBS). Cholesterol was reacted with NBS on solid support to result 1-methyl-19-norcholesta-1,3,5(10)-triene.

The reaction was attempted both on solid support as well as in solution phase. However no aromatization was observed in solution phase.

The reaction condition was optimized thoroughly giving emphasis on reaction temperature, solid phase (along with its amount) and recyclability of the catalyst.

Towards the probable mechanistic investigation it was found that, to have the aromatized product, C-3 containing groups donot act as leaving groups and both the C-4 hydrogens are required.

Applying the same reaction protocol, corresponding aromatized β-sitosterol analogue, 1-methyl-19-norstigmasta-1,3,5(10)-triene was prepared and 4β-hydroxy cholesterol produced 3-keto-4β,5α,6β-trihydroxy derivative.

Chapter III: *p*-TsOH-Mediated green transformations of di- and trihydroxy steroids toward diverse A/B-ring oxo-functionalization and evaluation of their cytotoxicity

Considering the significant usefulness of the ketosteroids, on the perspective of different chemical synthetic approaches and anticipated biological activities (after having a thorough review), the author became interested to undertake the above work. Thus, the present work was designed to utilize some oxysteroid biomolecules as the starting materials such as 4β-hydroxy- and 4β,7α-dihydroxy steroids. 4β-Hydroxy cholesterol is the most abundant cholesterol metabolite in human circulation and the degradation of cholesterol into bile acids involves 7α-hydroxylation as the rate determining step. As a consequence, 4β,7α-dihydroxy cholesterol owes prime attention in the metabolic research. The corresponding analogues of β-sitosterol, the major phytosterol available in nature, were also used as the starting materials. Moreover, considering the present day requirement of green chemistry applications, the

author tried to attempt the transformations on solvent-free solid supports and to our fortune, the results were satisfactory.

At a glance, the present work describes the solid support/*p*-TsOH-mediated oxidative transformations of 4β-hydroxy- and 4β,7α-dihydroxy derivatives into the corresponding oxo-functionalized steroids. Many of the oxo-steroids or keto steroids, furnished in the reactions, were interestingly isomeric through the involvement of the ring-A and -B of the steroid skeleton.

When 4β-hydroxy cholesterol was heated with *p*-TsOH on activated silica, three products isolated were analyzed as cholest-4-en-3-one, cholest-4-ene-3,6-dione and 5α-cholestane-3,6-dione.

The reaction protocol was optimized in detail, generalized through the application on similar different substrates, and efforts toward the mechanistic understanding were also evaluated.

The reaction was generalized by application of the same protocol on 4β-hydroxy β-sitosterol, 4β,7α-dihydroxy cholesterol and 4β,7α-dihydroxy β-sitosterol. 4β-Hydroxy β-sitosterol furnished three products, as was expected- stigmast-4-en-3-one, stigmast-4-en-3,6-dione and 5α-stigmastane-3,6-dione whereas 4β,7α-dihydroxy steroids resulted the corresponding steroidal- 4-ene-6-one; 3,5-dien-7-one; 4,6-dien-7-one; and 4,7-dione.

The anti-proliferative effect of the substrates and product molecules was estimated on protozoan parasite *Leishmania donovani* and the results are discussed. The most effective compound was found to be cholesta-3,5-dien-7-one which inhibited the *L. donovani* AG83 (MHOM/IN/83/AG83) promastigotes by 54% ($P<0.003$).

Chapter IV: Synthesis of A-ring modified friedelane triterpenoids and evaluation of their phytotoxicity

A-ring modified natural and synthetic friedelane triterpenoids along their bioactivities are thoroughly reviewed which, along with the consideration of the accelerating and versatile effect of $BF_3.OEt_2$/ Ac_2O led us finally to result a key-transformative reaction of friedelin to yield friedel-2-ene, friedel-3-enol acetate (the major product) and 2-keto-friedel-3-enol acetate.

Experiments showed $BF_3.OEt_2$ to be the only commonly available Lewis acid which performed the transformation and other common acetylating/ benzoylating agents instead of acetic anhydride were found ineffective.

A probable mechanism was postulated for the formation of the enol acetate and the same reaction protocol was applied on friedelin oxime and 3β-hydroxyfriedelane.

Then, a number of common reaction strategies, e.g., oxidation, reduction, acetylation, oximination, etc., were employed to achieve a library of C-2, C3- and C4-functionalised friedelin/ cerin derivatives. The derivatives were then biologically evaluated as their anticipated phytotoxicity taking *Oriza sativa* as the targeted entity. The sets of the isomeric compounds were very much helpful too to analyze the structure activity relationship studies (SAR) during the evaluation of the phytotoxic effect of the compounds. The phytotoxicity studies revealed the potential activity of the synthesized derivatives in comparison to the starting natural products which, indeed, imply presumably, the scope of the compounds to possess enhanced useful cytotoxicity and to use as agrochemicals.