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REVIEW

Sustainable approaches for steroid synthesis

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Abstract
Steroids are important scaffolds for the synthesis of molecules of pharmaceutical interest and constitute a distinct family of natural products. The demand for green and sustainable chemistry has fostered for the development of new reactions and chemical processes in steroidal chemistry. This review describes state-of-the-art approaches such as heterogeneous catalysis, microwave synthesis and microbial transformations for steroid synthesis.

Keywords Steroids · Synthesis · Green chemistry · Heterogeneous catalysts · Microwave · Microbial transformations

Introduction

Steroids, as an entrenched class of natural organic compounds, constitute the largest group of pharmaceuticals next to antibiotics. Steroids are employed as drugs for prevention and therapy for disorders like anti-inflammatory, diuretic, anabolic, contraceptive, antiandrogenic, progestational as well as anticancer agents for breast cancer and prostate cancer, and colon cancer (Morzycki 2011; Patel and Savjani 2015; Banday et al. 2010). Safety, less vulnerability to multidrug resistance (MDR) and extreme bioavailability are the important characteristics of steroid-based compounds. Steroids have future in pharmaceutical industry due to their growing significance to deal with a range of medical challenges based on their biological and pharmacological properties.

New synthesis methods are also needed in geochemical and petroleum research to identify fossil steroids as maturity parameters because actual methods involve multiple steps and toxic solvents (Bryselbout et al. 1998; Lichtfouse et al. 1990, 1994, 1998; Lichtfouse and Albrecht 1994). Many methods are available for the synthesis of steroids lack environmental, health concerns and resource conservation (Larsson 2014). Green chemistry has opened up innovative frontiers and prompted rapid improvements using more environment-friendly approaches as alternative sustainable routes for the development and synthetic transformations of steroids (Salvador et al. 2015; Huang et al. 2017; Kaplan et al. 2016; Cichowicz et al. 2015; Peterson 1985; Zlotos 2005; Misra et al. 2015; Wolfling 2007; Gupta and Mahajan 2015; Fenyvesi et al. 2018; Gude and Martinez-Guerra 2018; Dsikowitzky et al. 2017). Some of the imperative C19 and C21 steroid (Mesquita 2012) hormones and their selected analogues are shown in Figs. 1, 2 and 3.

Cholesterol (Fig. 4), an abundant steroid, contains 27 carbons, one hydroxyl group at C3, methyl groups at C13 and C10 designated as $18CH_3$ and $19CH_3$ correspondingly and one branch of eight aliphatic hydrocarbons on carbon C17.

Like most of the naturally occurring steroids, cholesterol has B/C and C/D diequatorial trans-fused (Mesquita 2012) rings with configuration at bridgehead position C8, C9, C13 and C14 as shown in Fig. 5: 8β–H, 9α–H, 13β–CH_3 and 14α–H. Two possible ring fusions are observed between rings A and B as configuration at C5 varies from one steroid to another. Some steroids are designated as 5α-steroids with A/B diequatorial (5α, 10β) trans-fused rings which explain 5α-configuration of the substituent at C5 position. In contrast, β-configuration of the C5 substituent is characterized by A/B axial–equatorial (5β, 10β) cis-fused rings.

Several oxidative chemical methods (Shan et al. 2009; Ouyang et al. 2014) have been established to provide significant intermediates for the synthesis of various biologically active steroid molecules. In numerous cases, heavy metals,

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fumed metal oxides, fumed silica are used to catalyze oxidative steps in steroids synthesis. Incorporation of green chemistry principles into some oxidative transformations allows paramount advances in synthetic chemistry when applied to steroidal compounds.

Heterogeneous catalysts

Heterogeneous catalysis plays a foremost part in the production of more than 80% of all chemical products and made a representative contribution to the decrement of environmental pollutants in the contemporary years (Mesquita 2012; Ouyang et al. 2014; Tong and Dong 2009).

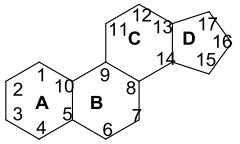


Fig. 1 Gonane: the simplest steroid

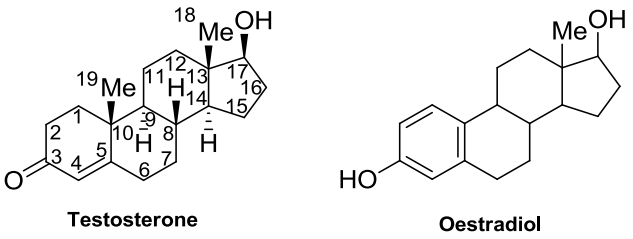


Fig. 2 Representative steroidal structures of testosterone and oestradiol

Ritter reaction with Starbon®400-SO_3H catalyst

In steroid chemistry, Starbon®400-SO_3H is used to catalyze acidic reactions like esterification of organic acids in aqueous medium, acylation of alcohols, amines and alkylations of aromatics (Budarin et al. 2007; Xing et al. 2007). It is a sulfonated mesoporous carbonaceous material prepared from mesoporous expanded starch as a precursor. In this ambience, using Starbon®400–SO_3H catalyst in Ritter reaction of 5β, 6β-epoxy-17-oxoandrostan-3β-yl acetate with nitriles sustained *vic*-*N*-acylamino-hydroxy products for the development of new chemical processes. Stereoselective

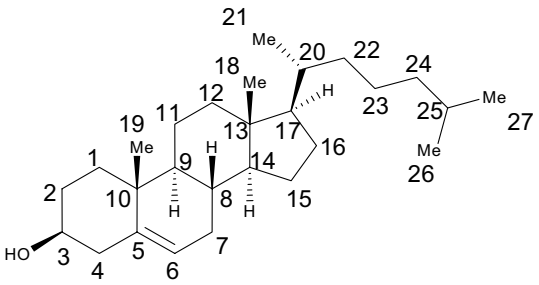


Fig. 4 Steroidal structures of cholesterol

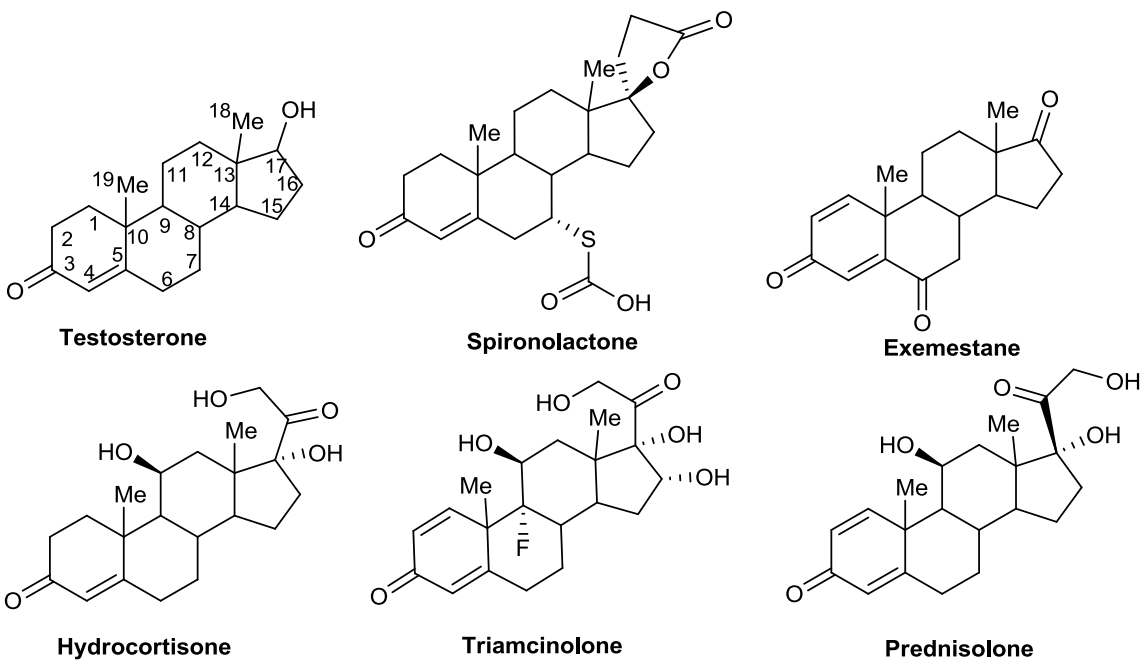


Fig. 3 Structure of important C_{19} and C_{21} steroid hormones and their selected analogues

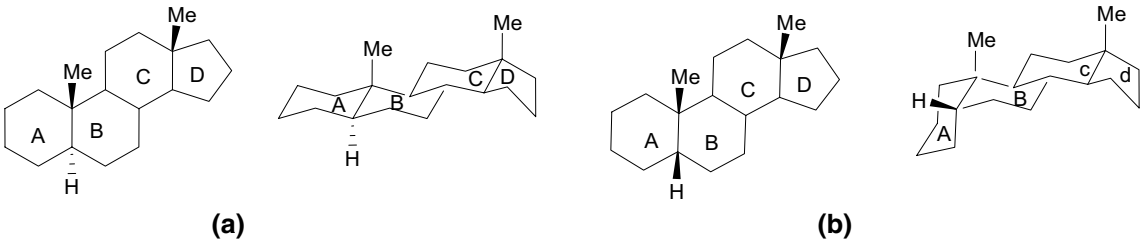
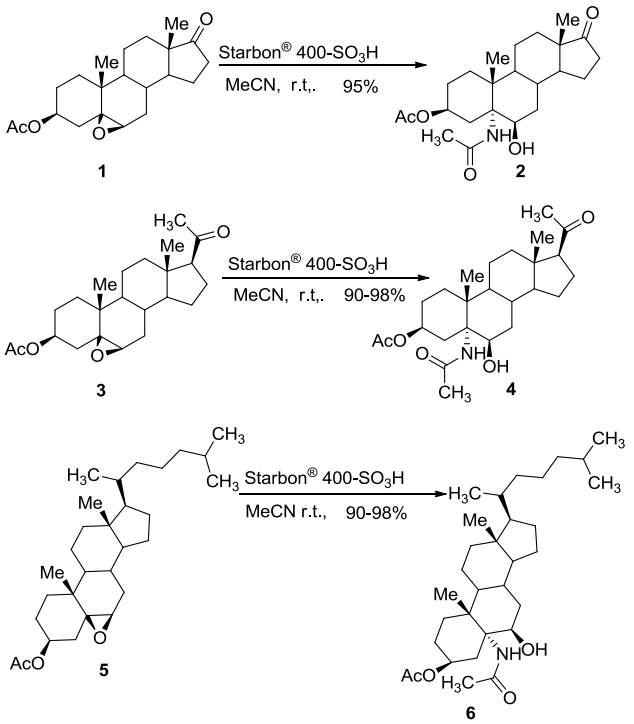


Fig. 5 Steroidal structures. **a** A/B diequatorial trans-fused rings. **b** A/B axial-equatorial cis-fused rings



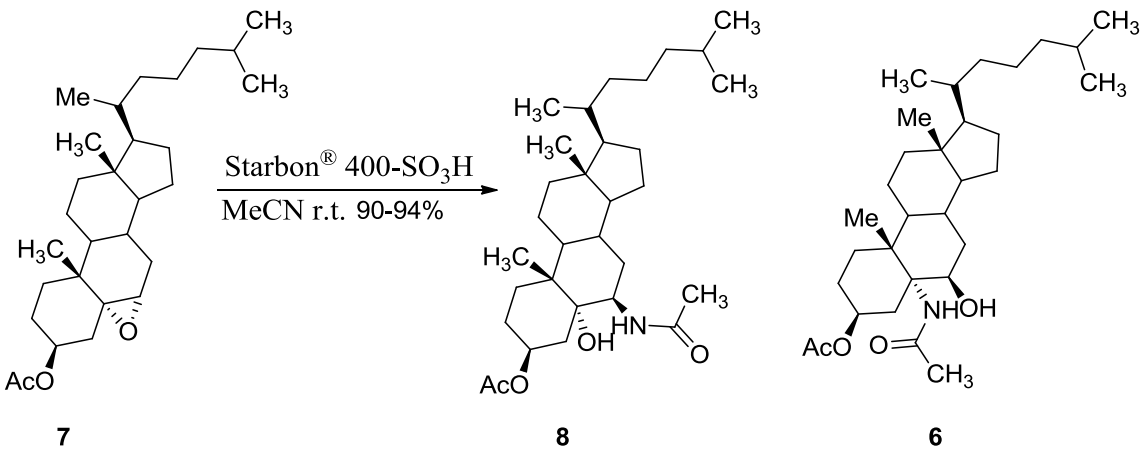
Scheme 1 Ritter reaction conditions with Starbon®400-SO_3H catalyst

trans-dial nucleophilic advance at C5 by the α-face in case of 5β, 6β-epoxy-17-oxoandrostan-3β-yl acetate and other 5β, 6β-epoxy steroids (5β, 6β-epoxy-20-oxopregnan-3β-yl acetate) and 5β, 6β-epoxycholestan-3β-yl acetate is attained for the corresponding acylamino-hydroxy products in a remarkable yield (Scheme 1).

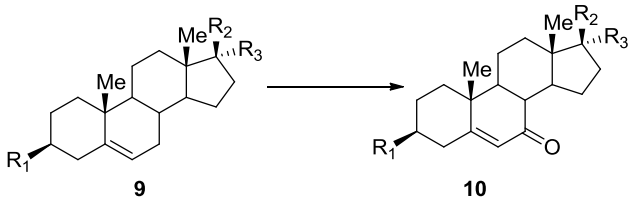
The trans-diaxial ring opening of 5α,6α-epoxycholestan-3β-yl acetate with nucleophilic attack at C6 and C5 positions (Scheme 2) through β- and α-face afforded a mixture of stereoisomers, the 6β-acetamido-5α-hydroxycholestan-3β-yl acetate **8** and stereoisomer **6**.

Allylic oxidation with heterogeneous catalyst

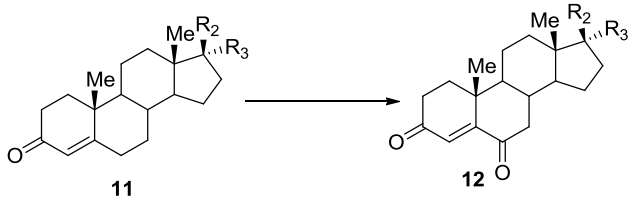
Conventionally, allylic oxidation of Δ^5-steroids has been achieved with various obnoxious and environmentally unsafe complexes (Scheme 3) like CrO_3-pyridine, chromium trioxide, pyridinium dichromate (PDC), pyridinium chlorochromate (PCC), sodium chromate and sodium dichromate (Wendell and Edward 2016; Salvador et al. 2006, 2012; Bulman Page and McCarthy 1991; Salvador and Silvestre 2005; Salvador et al. 2011).



Scheme 2 Ritter reaction catalyzed by Starbon®400-SO_3H for 5α,6β-epoxycholestan-3β-yl acetate



Scheme 3 Allylic oxidation of Δ^5-steroids to Δ^5-7-oxosteroids



Scheme 4 Allylic oxidation of Δ^5-3-ketone-steroids to corresponding Δ^4-3,6-diketone-steroids

In recent times, several heterogeneous catalysts such as $KMnO_4/SiO_2$ in benzene or chromium (VI) adsorbed on SiO_2/ZrO_2, cobalt (II), copper(II), manganese(II) and vanadium(II) immobilized on silica and $BiCl_3$/montmorillonite K-10 in combination with *tert*-butyl hydroperoxide as an oxidant have been used for allylic oxidation of Δ^5-steroids. As environmentally safe advances, the oxidation of steroidal olefins compounds to α,β-enones has also been conceded with household bleach and aqueous *tert*-butyl hydroperoxide at ambient temperature. Dirhodium caprolactamate ($[Rh_2(cap)_4]$) catalyst in the presence of 70% *tert*-butyl hydroperoxide in water has been reported recently for the preparation of several steroids (Scheme 4) like Δ^4-3,6-ketones (Doyle et al. 2012).

Allylic oxidation with dirhodium (II, II) caprolactamate

Recently, Doyle et al. (2012) profoundly depicted the methods for achieving the efficient allylic oxidation of 7-keto steroidal molecules applying dirhodium (II, II) paddlewheel complexes and in particular dirhodium carboximate (Fig. 6) and *t*-BuOOH as catalysts under aqueous conditions in comparison to anhydrous methods.

Oxidation of alkenes at allylic position to unsaturated carbonyl compounds is achieved by hydrogen abstraction by *t*-butylperoxy radicals produced from dirhodium (II) complexes. The proposed reaction mechanism for $Rh_2(cap)_4$-mediated allylic oxidation is described in (Fig. 7) taking cyclohexene as the substrate. The oxidation reactions of steroids (testosterone, 4-androstene-3,17-dione, 4-cholesten-3-one) performed by 70% aqueous solution

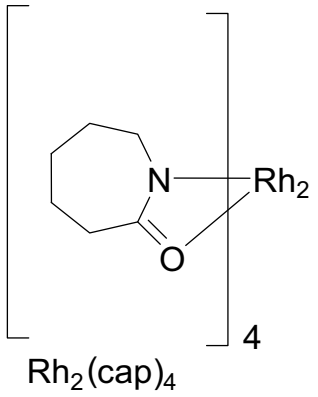


Fig. 6 Structure of dirhodium (II, II) caprolactamate

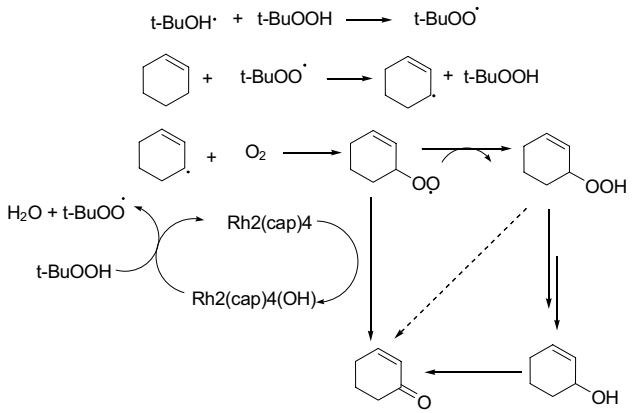
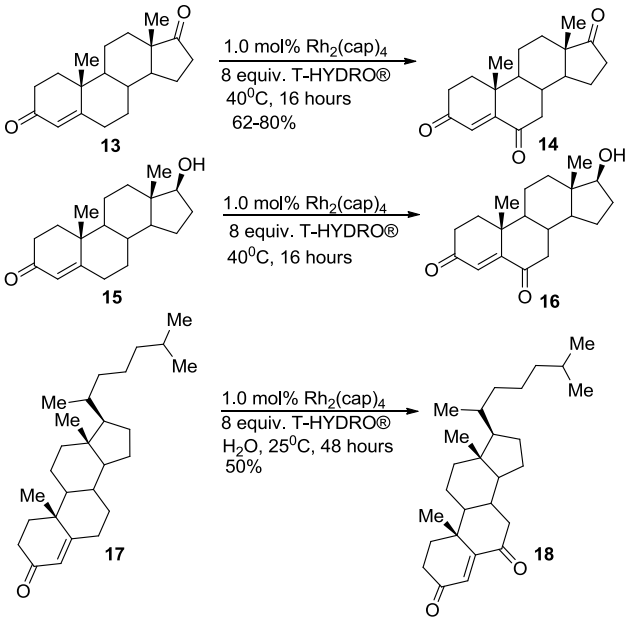


Fig. 7 Preferred reaction mechanism for $Rh_2(cap)_4$-mediated allylic oxidation

of *tert*-butyl hydroperoxide (T-HYDRO®) catalyzed by $Rh_2(cap)_4$ are shown in Scheme 5.

Allylic oxidation with bismuth (III) and cobalt (II) salts

Latterly, environment-friendly catalysts such as bismuth (III) and cobalt (II) salts played a key role in the allylic oxidations of steroids at the 7-position in organic synthesis of pharmaceutical interest. Allylic oxidation of a variety of Δ^5-steroids using bismuth (III) salts-based several heterogeneous bismuth catalysts in combination with *t*-BuOOH has been reported by Salvador et al. (2006, 2012), Bulman Page and McCarthy (1991) and Salvador and Silvestre (2005). $BiCl_3$/*t*-BuOOH catalyst system is used for allylic oxidation of Δ^5-steroids to produce corresponding Δ^5-7-oxosteroids (Salvador et al. 2011; Parish et al. 2004) and proved to be very (Scheme 6) selective as momentous epoxidation of the double bond and secondary hydroxyl group oxidation can be avoided. Further $BiCl_3$/*t*-BuOOH

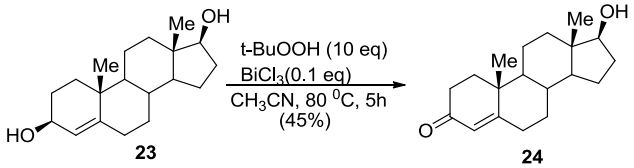


Scheme 5 Allylic oxidation of Δ^4-3-ketone-steroids to corresponding Δ^4-3,6-diketone-steroids with dirhodium (II, II) caprolactamate

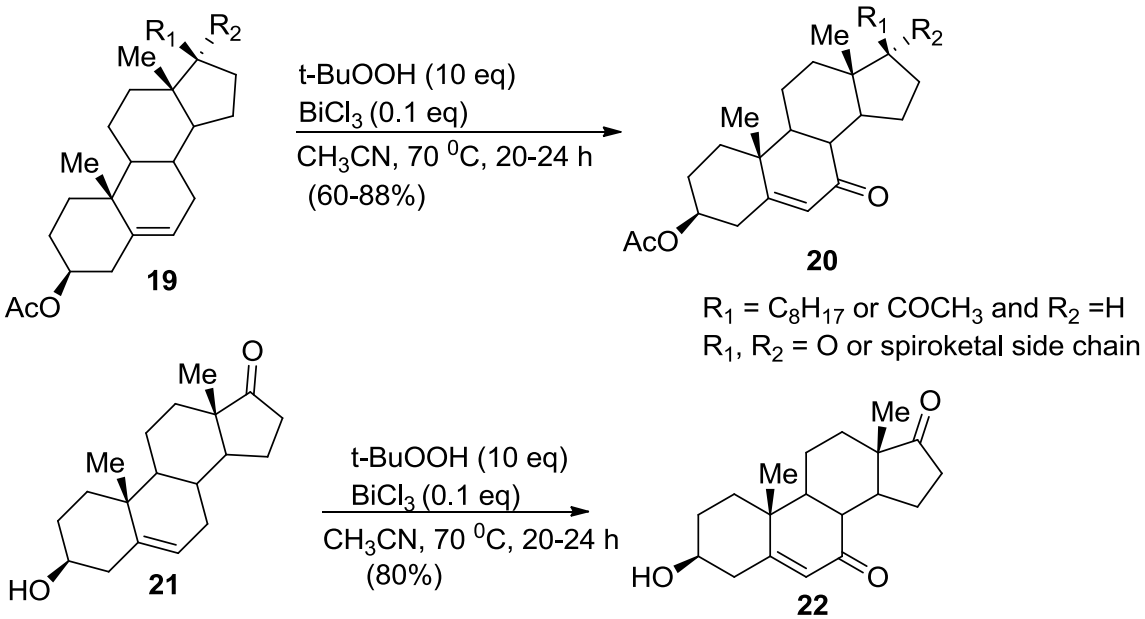
system used in the allylic alcohol oxidation (Scheme 7) of androst-4-ene-3β,17β-diol provided an important hormone testosterone in 45% yield.

Allylic oxidation of steroids at 7-position with heterogeneous Co(II) catalysts **1, 2, 3** has also been reported as a sustainable method (Fig. 8) (Salvador and Clark 2001).

It is pertinent to mention that thermal and chemical stability of employed supports all through the reaction process and batch reactions during the separation phase, accessibility and good dispersions of the active sites in an organic reaction arbitrates the performance of the supported catalyst. Frequently used inorganic supports are zeolites, silica, polymers, hydroxyapatite, zirconia, carbons, and all these supports have high surface areas (100–1000 m^2/g) with average pore diameters ranging from the micro-zeolites to some micro-porous silica (Gupta and Paul 2014). Δ^5-steroids can be selectively oxidized at the allylic position to 5-en-7-ones in high yield using silica-supported cobalt acetate along with *t*-butyl hydroperoxide as an oxidant. Under similar reaction conditions, **catalysts 2** and **3** can be recycled with small decline in the product yield (80% for recycled **catalyst 2** and 81% for recycled **catalyst 3**) (Salvador and Clark 2001). The catalytic method is also effective in the presence of an oxidative vulnerable secondary alcohol group (Scheme 8), as well as when applied to unsaturated Δ^4-steroids, the steroid **33** is oxidized to the alcohol product **34** with impressive selectivity (71%) and **36** gives the testosterone acetate **37** in 70% yield.



Scheme 7 Selective allylic alcohol oxidation of steroids by $BiCl_3$/*t*-BuOOH



Scheme 6 Bismuth (III) salt-catalyzed allylic oxidation of Δ^5-steroids

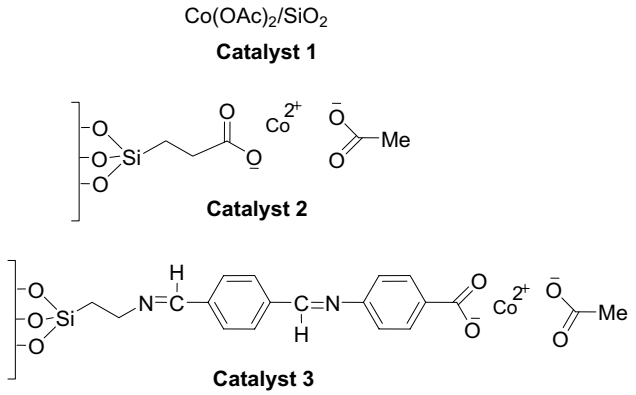


Fig. 8 Structure of silica-supported Co(ll) heterogeneous catalysts

Bismuth reagents

Over the last decade, bismuth (III) salts (Salvador and Silvestre 2005, 2006) for the design of eco-catalysts and a large number of methods involving the use of Bi(III) compounds in organic synthesis of pharmaceutical interest have been reported (Salvador and Silvestre 2006). Bi_2O_3/CH_3COOH along with in situ preparation of efficient and selective oxidant $Bi(OAc)_3$ causes selective oxidation of α-hydroxy ketone to corresponding diketo due to its chemical selectivity in various steroids. Further dehydrohalogenated 20, 21-diketo product **41** was accomplished from oxidation of 20,21-ketol group of a 21-chloromethyl-pregnane (Angello et al. 1963) derivative (Scheme 9) in Bi_2O_3/CH_3COOH mixture. Bi_2O_3/CH_3COOH system has also been used for the oxidation of the 11-keto-12β hydroxyl moiety (Scheme 10) of a hecogenin derivative (Djerassi et al. 1954) for the preparation of an intermediate in the synthesis of cortisone.

Acylation of cholesterol with bismuth (III) salts

Recently, several bismuth (III) salt catalysts have been reported for acylation (Orita et al. 2000, 2001; Stephens et al. 2003), and $Bi(OTf)_3{\cdot}xH_2O$ in the presence of acetic anhydride (Scheme 11) is used for the acetylation of cholesterol. Regardless of sterically hindered 12α-hydroxy group, all the three hydroxyl groups of cholic acid methyl ester are remarkably converted to the analogous acetoxy groups in outstanding yield.

Tetrahydropyranylation of cholesterol with bismuth (III) salts

Tetrahydropyranylation of the secondary hydroxyl groups in cholesterol derivatives (Stephens et al. 2003; Khan et al. 2005) has been achieved with 3,4-dihydro-2*H*-pyran in the presence of $Bi(OTf)_3{\cdot}xH_2O$ (Scheme 12).

Microwave-assisted steroid synthesis

The short reaction times and expanded reaction range offered by microwave-assisted organic synthesis are appropriate to the increased demands in chemical industry.

Microwave-promoted one-pot synthesis of novel A-ring-fused steroidal dehydropiperazines

Microwave irradiation-based preparation of ring-A-fused 3,4-position steroidal dehydropiperazine is recently reported by Borthakur et al. (2008). In one-pot reaction, annulations are commenced from easily available 3-keto-4-en steroids (testosterone acetate, 4-androsten-3,17-dione, progesterone, 24-ethyl 4, 22-cholestadiene-one) with ethylenediamine in environmentally innocuous manner. Base-catalyzed aerial oxidation of the C6 methylene group is key stage pursued by cyclocondensation of ethylenediamine via Michael addition reaction to afford dehydropiperazine adducts **49a–f** (Scheme 13). In the proposed mechanism for the formation of dehydropiperazine derivatives (Scheme 14) under basic conditions, enolate intermediate facilitates aerial oxidation of C6 allylic protons to afford diketo intermediate followed by cyclocondensation of ethylenediamine with diketo intermediate pursued with Michael addition and autooxidation.

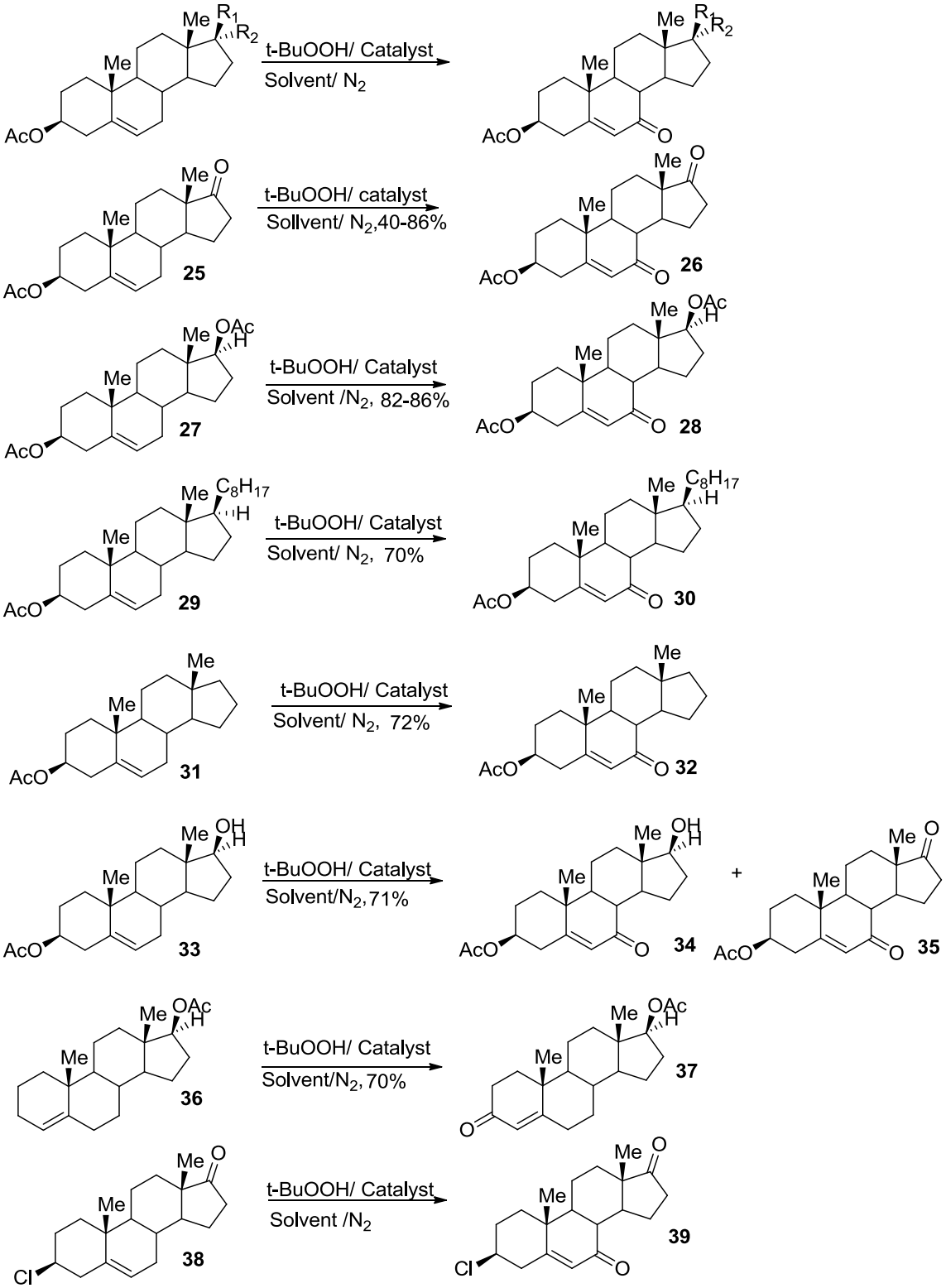
Microwave-promoted deprotection of 3-one-oximes to 3-keto steroids

A catalytic procedure using 10% $BiCl_3$ under microwave irradiation for deprotection of 5α-cholestan-3-one-oxime for the generation of the corresponding 3-keto-steroid, e.g., 5α-cholestan-3-one in 80% yield has been reported (Boruah et al. 1997) (Scheme 15).

Similarly, microwave-based green chemistry has been used for a variety of condensations such as deprotection, esterification and silylation reactions in steroids (Lidstrom et al. 2001), Wittig olefination of 3-ketosteroids, (Spinella et al. 1997) basic amide hydrolysis (Dayal and Ertel 1998) using alkali, silylation reaction (Lidstrom et al. 2001) of secondary alcohol using *tert*-butyldimethylsilyl chloride (TBDMS) and esterification (Lami et al. 1999) of acids using methanesulfonic acid (Scheme 16).

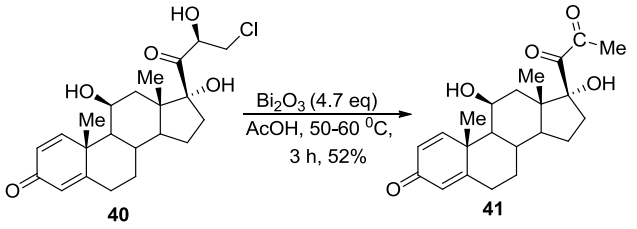
Microwave-promoted preparation of steroidal chalcones

In 2012, Kakati et al. (2013), Silvestre et al. (2016), Bianchi and Baulieu (2012) and Ornelas et al. (2005) reported a solvent-free coupling of pregnenolone acetate with

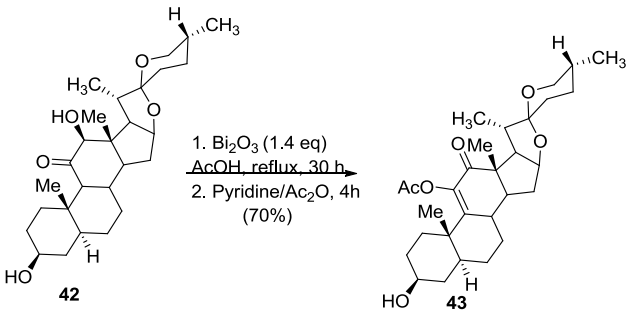


Scheme 8 Allylic oxidation of Δ^5-steroids to corresponding Δ^5-7 ketone-steroids with silica-supported Co(II) heterogeneous catalyst

different aldehydes to build up a library of novel pregnenolone steroidal hybrids possessing potential antimicrobial activities against pathogens (Scheme 17). Claisen–Schmidt condensation of pregnenolone acetate with variously substituted benzaldehydes has been carried out in the presence of I_2–Al_2O_3 as catalyst under microwave reaction conditions.



Scheme 9 Bi_2O_3/AcOH oxidation of the 20, 21 ketol group of a 21-chloromethyl-pregnane derivative



Scheme 10 Bi_2O_2/AcOH oxidation of the 11-keto-12β-hydroxy moiety of a hecogenin derivative

Microwave-promoted preparation of steroidal ring-D-fused–quinoline hybrid

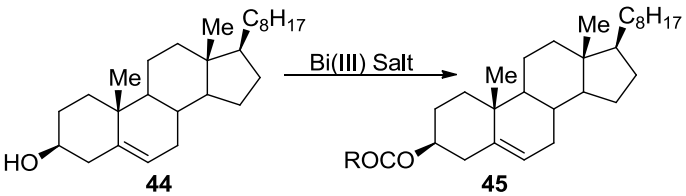
Efficient synthesis of novel steroidal D- and A-ring-fused–quinoline hybrids in the estrone and 5α-androstane series has been reported by Frank et al. by the reaction of β-chlorovinyl aldehydes with different aryl amines in polar aprotic solvent under microwave conditions (Scheme 18) (Baji et al. 2016). The electronic and steric characters of the substituents on the anilines and different reactivities of rings D and A sterane skeleton control the rates and yields of the desired products in one-pot catalyst-free syntheses. For the preparation of D-fused quinoline derivatives, simultaneous addition of $POCl_3$ and DMF to an ice-cold solution of estrone 3-methyl ether in chloroform followed with subsequent reflux afforded a β-chlorovinyl aldehyde with the Vilsmeier–Haack reagent, together a 17-chloro-derivative as by product. The microwave-assisted solvent-free reaction of β-chlorovinyl aldehyde (LaFrate et al. 2008) with aniline containing electron-donating groups (EDG) in the para-position on the aromatic moiety furnished the corresponding products in reasonable yields which may be attributed to the higher rigidity and sterically more hindered character of the five-membered ring D, primarily due to the presence of angular methyl group on C13.

Microwave-promoted preparation of steroidal ring-A-fused–quinoline hybrid

For similar reactions on ring A of sterane skeleton, 17β-acetoxy-5α dihydrotestosterone was reacted with Vilsmeier–Haack reagent via **Method A** to afford bis-formylated as the main product with minor desired β-chlorovinyl aldehyde. The desired β-chlorovinyl aldehyde was obtained by means of **Method B** in 78% yield by performing the reaction with Vilsmeier–Haack reagent at 25 °C for 2 h. Distinctly substituted anilines with electron-donating groups (EDGs) readily underwent cyclization with β-chlorovinyl aldehyde in dimethylformamide (DMF) to furnish ring-A-fused quinolines (Gogoi et al. 2012) in excellent yields (Scheme 19) when the reaction was carried out under microwave irradiation.

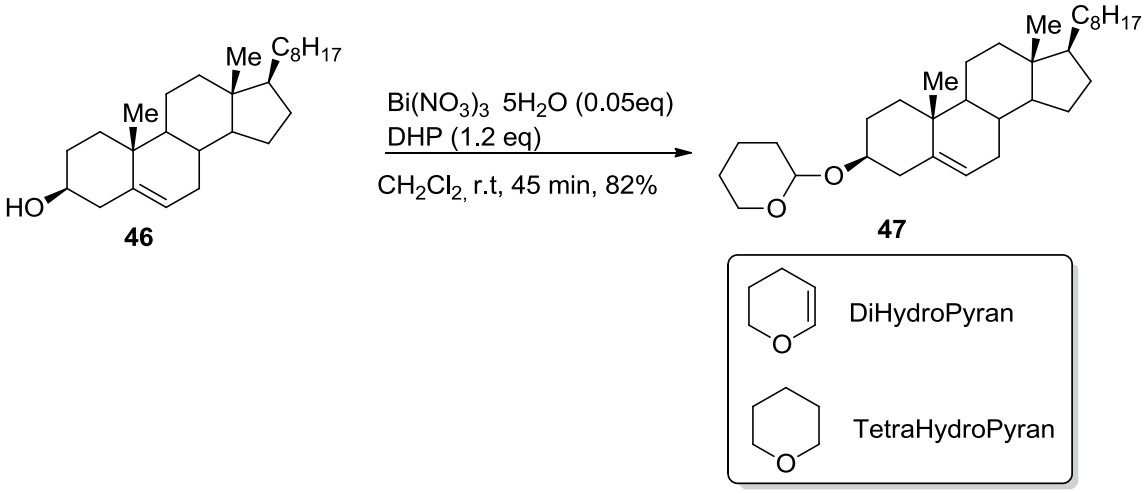
Microwave-assisted Baeyer–Villiger oxidation of steroidal ketones

Baeyer–Villiger oxidation of several steroids in the presence of catalyst $Ca[B(C_6F_5)_4]_2$ and hydrogen peroxide under microwave irradiation turned out the corresponding esters/lactones as reported by Borah and Chowdhury (2011). Baeyer–Villiger oxidation of 17-oxo-5α-androstan-3β-yl acetate

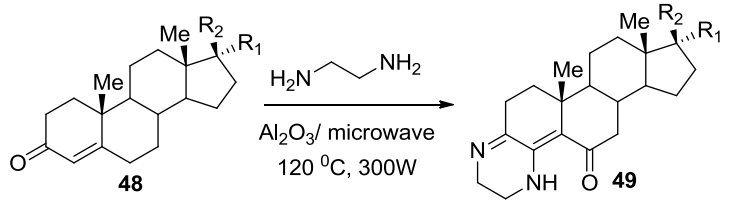


R = CH_3: $Bi(OAc)_3$ (1.1 (eq), neat , 160 ^{0}C, 25 h, 48%
$Bi(OTf)_3.XH_2O$ (0.01 eq), Ac_2O (10eq), THF, 25^{0}C, 1h, 97%
BiOCl (0.005 eq), CH_3COCl (2eq), CH_2Cl_2, rt, 30 min, 96%
R = t-Bu: $Bi(OTf)_3.xH_2O$ (0.03eq), (t-BuCO)$_2$O (1.5 eq, CH_2Cl_2, 25^{0}C, 5h, 97%

Scheme 11 Acetylation and pivaloylation of cholesterol with bismuth (III) salts



Scheme 12 Bismuth(lll) salt-catalyzed tetrahydropyranylation of cholesterol



48a, R_1 =H, R_2=-CH(CH)$_3$-$CH_2CH_2CH_2CH(CH_3)_2$
48b, R_1 = H, R_2 = OH
48c, R_1 = H, R_2 = $OCOCH_3$
48d, R_1 = R_2 = O
49e, R_1= H, R_2 = $COCH_3$
48f, R_1 = H, R_2 = -CH(CH_3)-CH=CHCHCH(CH_3)$_2$ (with CH_2CH_3)

49a, R_1 =H, R_2=-CH(CH)$_3$-$CH_2CH_2CH_2CH(CH_3)_2$
49b, R_1 = H, R_2 = OH
49c, R_1 = H, R_2 = $OCOCH_3$
49d, R_1 = R_2 = O
49e, R_1 =H, R_2= $COCH_3$
49f, R_1 = H, R_2 = -CH(CH_3)-CH=CHCHCH(CH_3)$_2$ (with CH_2CH_3)

Scheme 13 Synthesis of steroidal dehydropiperazines from corresponding 3-keto-4-en steroids

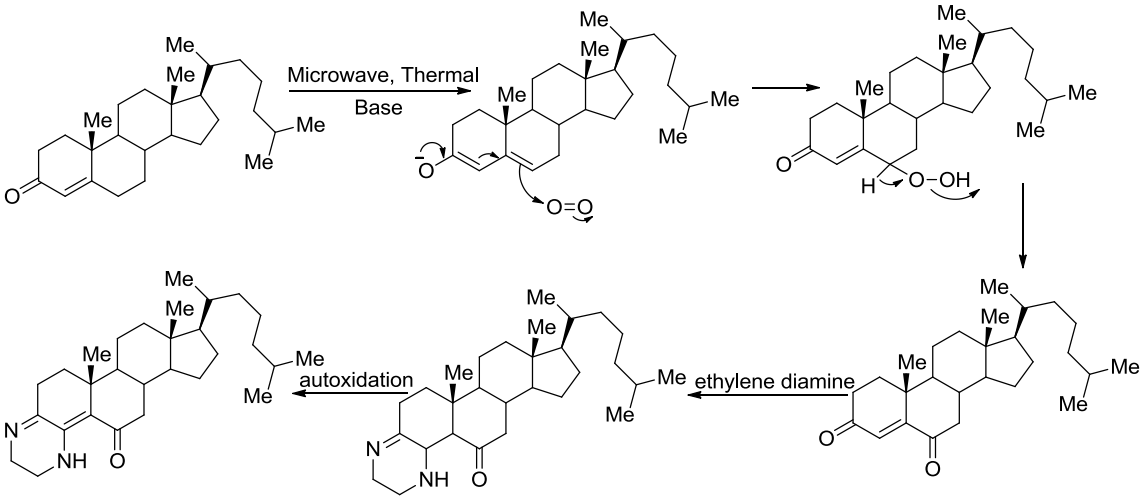
by *meta*-chloroperoxybenzoic acid (MCPBA) under microwave irradiation is shown in Scheme 20.

Microwave-assisted synthesis of steroidal oxime ethers

Incorporation of one or more hetero-atoms in the steroid moiety to produce novel steroidal derivatives with diverse applications has also been achieved using microwave irradiation. In this context, Alam and Lee (2015) reported the synthesis of biologically active steroidal oxime ether 7-(2′-aminoethoxyimino)-cholest-5-ene and its derivatives via facile microwave-assisted green solvent-free reaction technology. The new convenient sustainable, reproducible protocol with short reaction time resulted in a remarkable improvement in the synthetic efficiency (85–93%) and high purity using basic alumina as a solid support (Scheme 21).

Biotransformations

A large number of steroids have been synthesized by exploiting microorganisms for biotransformations. Enzymes catalyzed reactions in microbial transformations include chemical reactions like oxidation, reduction, hydrolysis and degradation, formation of C–C or C-hetero-bonds. Several advantages in selecting microbial reactions as alternative to conventional synthesis are (a) to functionalize specific positions in the molecule which are not normally possible



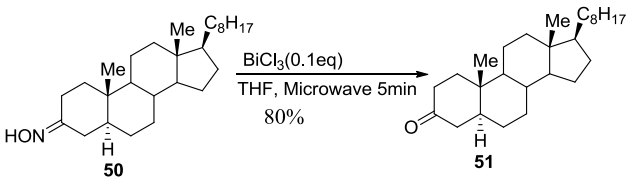
Scheme 14 Proposed mechanism for the formation of dehydropiperzine derivative

by chemical methods and (b) stereospecific or regiospecific introduction of oxygen functionality or other substituent.

Microbial hydroxylation by Aspergillus and Rhizopus species

For the first time, Hosseinabadi et al. (2015) reported that various sites of steroid precursors can be hydroxylated with different *Asperigillus* species, which is difficult to attain by chemical methods for the production of valuable steroids with diverse pharmacological properties, e.g., three valuable hydroxylated metabolites: 11α-hydroxyprogesterone, 14α-hydroxyprogesterone and 21-hydroxyprogesterone can be obtained after bioconversion of progesterone (a C21 steroid hormone) by filamentous fungi *Aspergillus brasiliensis* (Fig. 9). Moreover, hydroxylation at specific positions in steroids increases the biological activity, e.g., products of 11α-hydroxylation and 14α-hydroxylation in the corticosteroid synthesis possess anticancer properties (Fernandes et al. 2003; Zohri and Galil Abdel 1999).

Further, a 31-step chemical synthesis of cortisone (Scheme 22) from bile acid has been achieved with regiospecific and enantiospecific microbial hydroxylation (Peterson 1985).



50 **51**

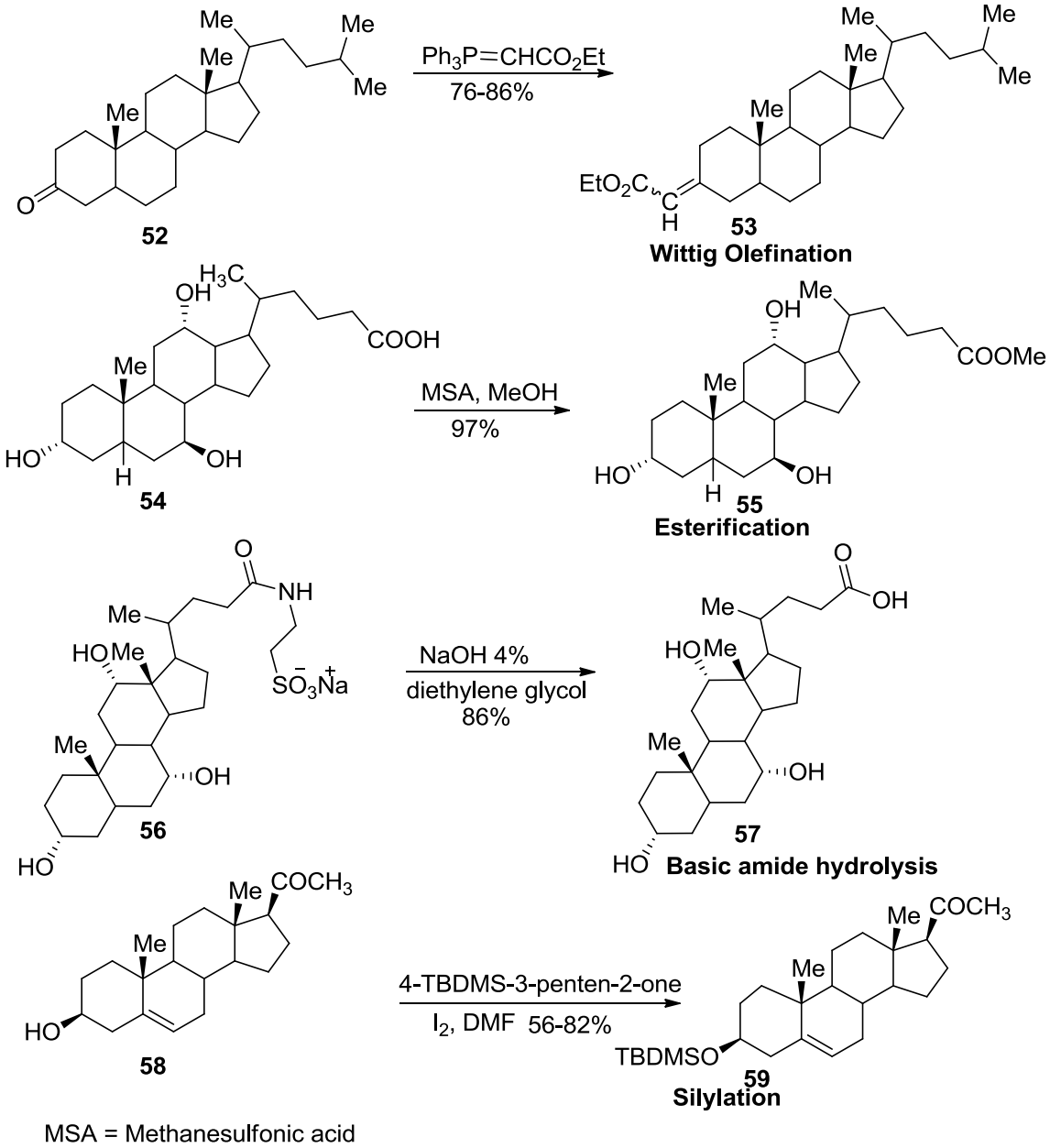
Scheme 15 Microwave-promoted deprotection of 3-one-oximes to 3-keto steroids

β-oxidation cycle reactions

Accessibility of raw materials is one of the fundamental challenges associated for the production of steroidal drugs so majority of steroid-based drugs are synthesized by semi-synthetic routes (Dewick 2009). Biological transformations of natural substrates via β-oxidation reactions (Swizdor et al. 2012) are the focus of synthetic routes for biologically active compounds. The pharmaceutical industry is involved significantly in the selective degradation of sterol side chain (Fig. 10) because this results in the formation of steroid intermediates of therapeutic application which can be used as building blocks for the advance synthesis of bioactive steroids.

Microbiological degradation of side chain of sterols

In majority of steroids, double bond at C5 and a hydroxyl group at 3β-position can be easily converted to a 4-en-3-oxo moiety. Selective degradation of the 17β aliphatic (Smith 1984; Dunn et al. 2010) side chain of many sterols which is not possible effectively by chemical means can be carried out with microbial transformation due to selectivity of enzymes. Several strains of gram-positive (*Pseudomonas, Rhodococcus, Mycobacterium, Streptomyces, Brevibacterium*) and gram-negative (*Pseudomonas, Comamonas, Bukholderia, Chromobacterium*) bacteria can utilize sterols as the sole carbon source and produce carbon dioxide and water as the final product of microbial degradation of sterols (Scheme 23). The

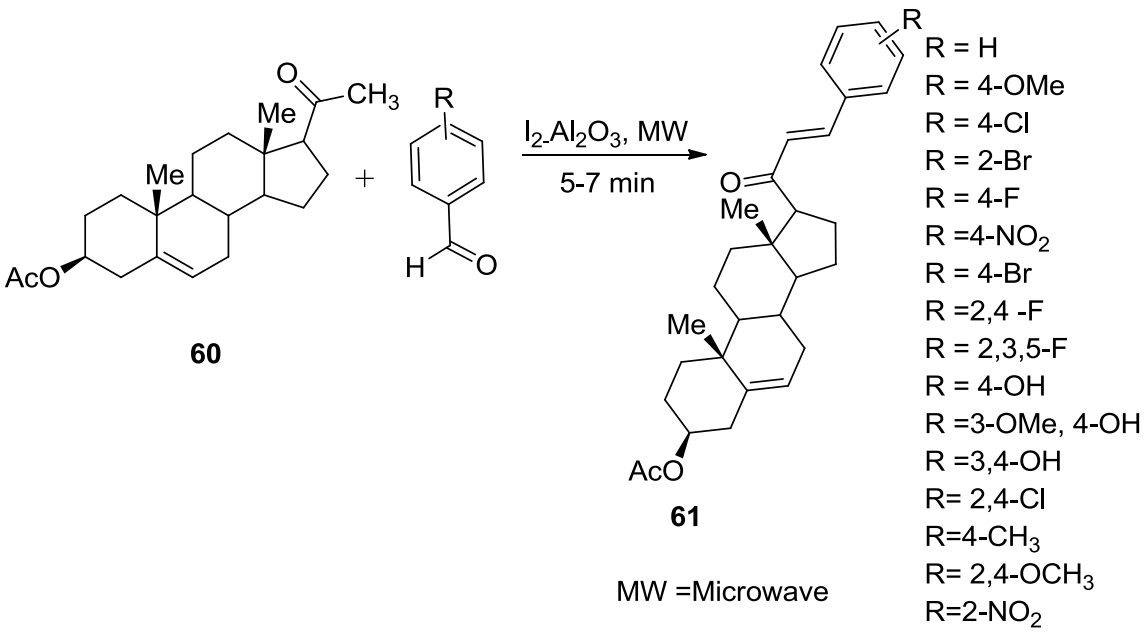


Scheme 16 Microwave-promoted Wittig olefination, esterification, amide hydrolysis, silylation in steroids

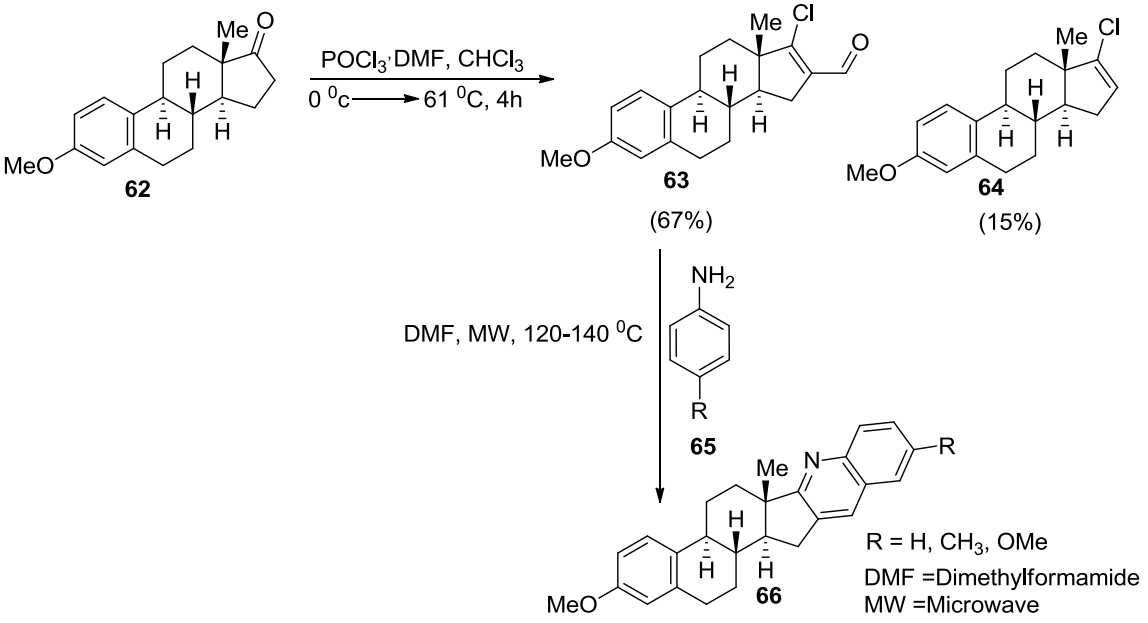
other identified metabolites are synthetically useful C19 steroids: androsta-4-en-3,17-dione (AD), androsta-1,4-dien-3,17-dione (ADD), 9α-hydroxy-androsta-1,4-dien-3,17-dione(9α-hydroxy-ADD) and other C22 products: 20-carboxy-pregna-4-en-3-one, 20-carboxy-pregna-4,17(20)-dien-3-one. AD is obtained as the outcome of oxidative degradation of the side chain of cholesterol after subsequent cleavage of propionyl-CoA, acetyl CoA and propionyl -CoA, respectively.

Biotransformation of resibufogenin and cinobufagin by *Pseudomonas aeruginosa*

Pseudomonas aeruginosa as 1.860 present versatile means of biotransformation for structural modification of resibufogenin and cinobufagin to four (Hegazy et al. 2015; Zhan et al. 2003) dehydrogenated products, 3-keto-resibufogenin **87**, 3-keto-cinobufagin **85**, 3-keto deacetylcinobufagin **90** and deacetyl cinobufagin **88** shown in Scheme 24.



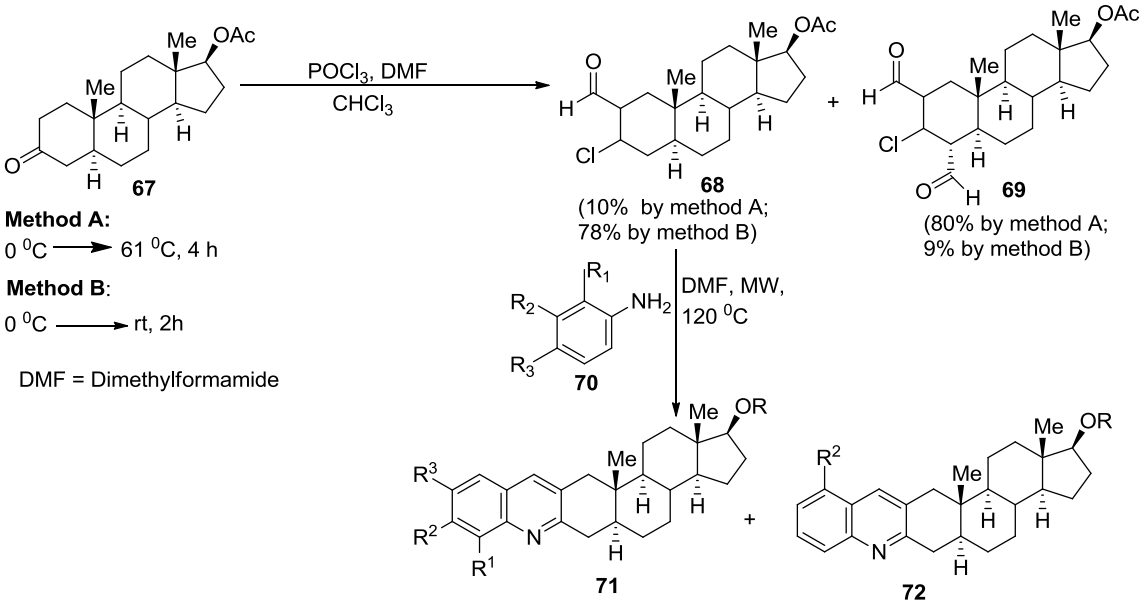
Scheme 17 Microwave-promoted synthesis of chalconoyl pregnenolones



Scheme 18 Microwave-promoted synthesis of steroidal ring-D-fused–quinoline hybrid

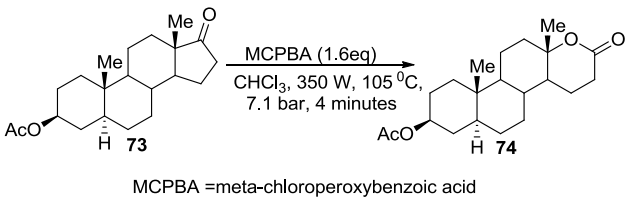
Conclusion

Steroid chemistry has been the focus of research for over one hundred years. With every passing day, there are reports of the isolation, characterization and synthesis of new compounds of new biological evaluations. The attention given to steroid molecules is justified by their biological properties that make them useful in medicinal

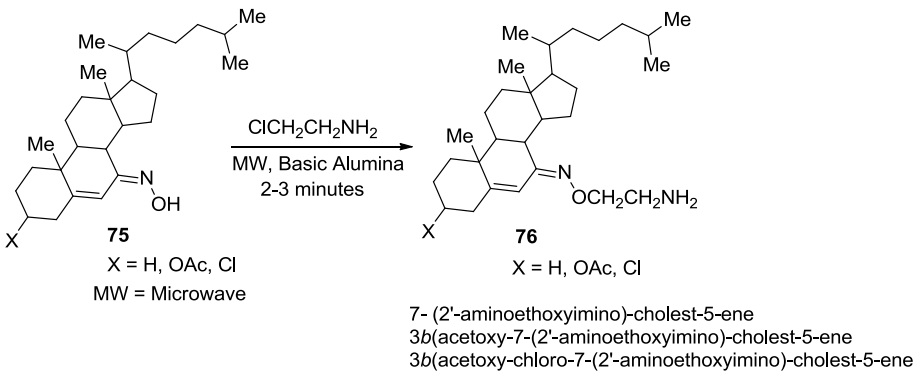


Scheme 19 Microwave-promoted synthesis of steroidal ring-A-fused–quinoline hybrid

chemistry. Although there are abundant conventional chemical reactions known with wide applicability in steroid chemistry, these reactions often suffer from disadvantages such as handling toxic, sensitive and expensive reagents, difficult workups, low yields, weak selectivity and lack of catalytic methods. For these reasons, the development of new chemical processes in steroid chemistry that use environmental-friendly, cheap and easily available reactants as well as mild reaction conditions would be of great interest. Green chemistry addresses such challenges by providing novel environmentally and ecologically benign reactions that can maximize the production of the desired products and minimize side reactions. The incorporation of the discussed procedures in the design of large-scale synthetic approaches for the preparation of selected steroids in a near future is very well expected.



Scheme 20 Baeyer–Villiger oxidation of steroidal ketone to steroidal lactones



Scheme 21 Microwave-based synthesis of steroidal oxime ethers

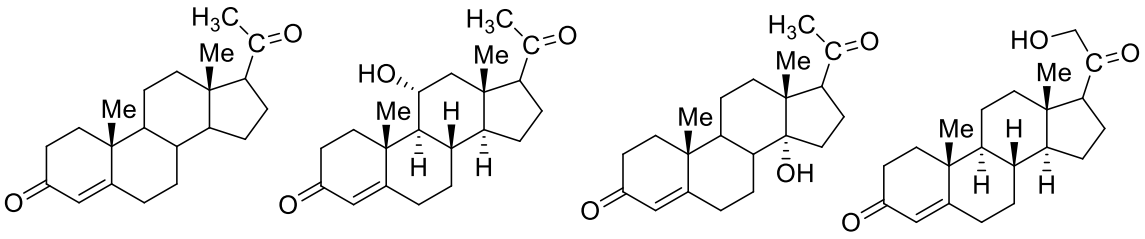
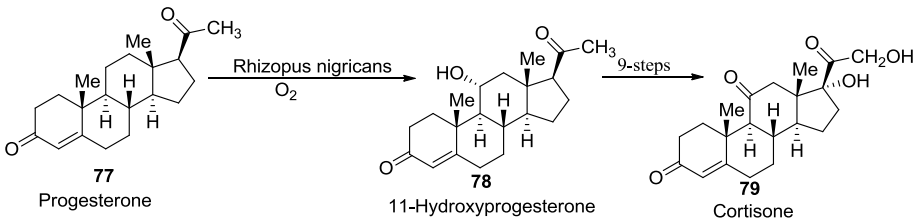


Fig. 9 Structure of progesterone and its metabolite



Scheme 22 Cortisone synthesis

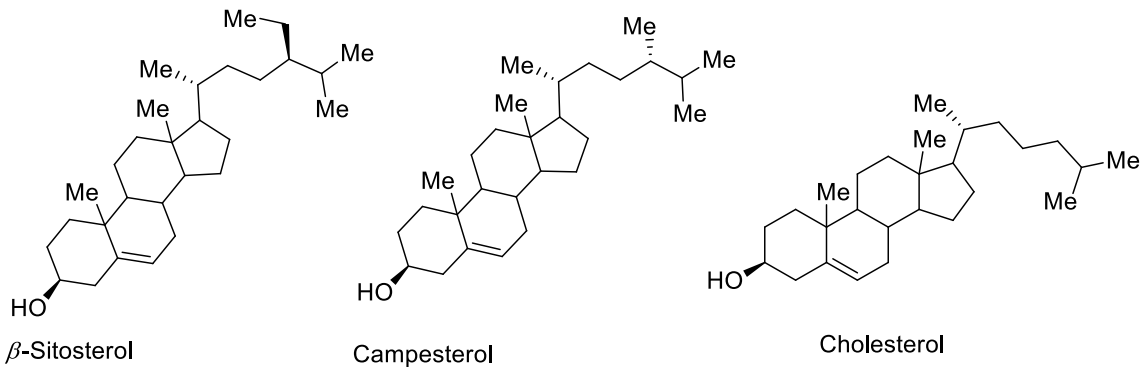
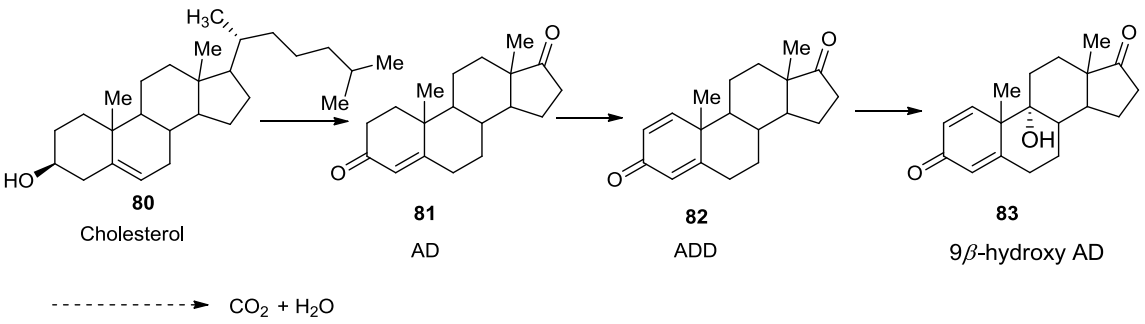
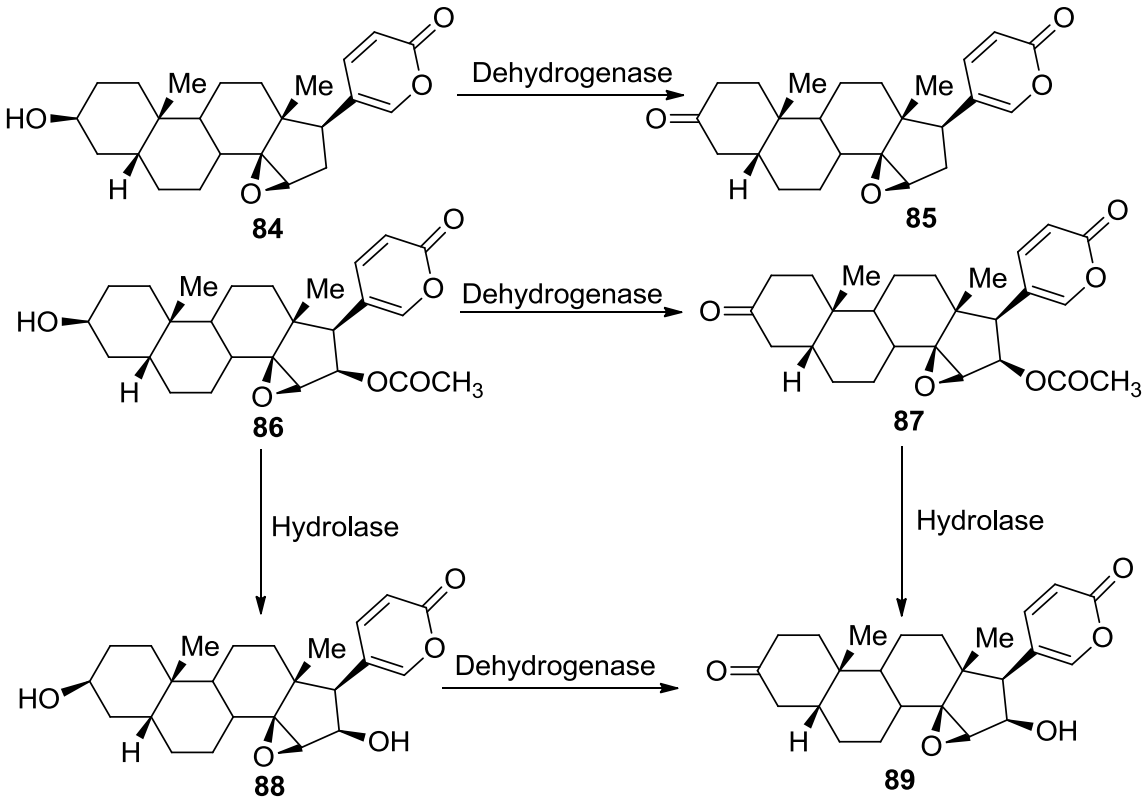


Fig. 10 Structures of (phyto)sterols with a saturated side chain



Scheme 23 Microbial catabolic pathway of cholesterol (valuable steroid drug intermediates)



Scheme 24 Biotransformation pathways of resibufogenin and cinobufagin by *Pseudomonas aeruginosa*

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References

Alam M, Lee DU (2015) Eco-friendly synthesis, physiochemical studies, biological assay and molecular docking of steroidal oxime-ether. EXCLI J 14:394–407. https://doi.org/10.17179/excli2014-675

Angello EJ, Figdor SK, Hughes GMK, Ordway HW, Pinson R Jr, Bloom BM, Laubach GD (1963) A Stereospecific Synthesis of C-21-Methylated Corticosteroids. J Org Chem 28:1531–1539. https://doi.org/10.1021/jo01041a022

Baji A, Gyovai A, Wolfling J, Minorics R, Ocsovszki I, Zupko I, Frank E (2016) Microwave-assisted one-pot synthesis of steroid–quinoline hybrids and an evaluation of their antiproliferative activities on gynecological cancer cell lines. RSC. Adv. 6:27501–27516. https://doi.org/10.1039/c6ra03910c

Banday AH, Mir BP, Lone IH, Suri KA, Kumar HMS (2010) Studies on novel D-ring substituted steroidal pyrazolines as potential anticancer agents. Steroids 75:805–809. https://doi.org/10.1016/j.steroids.2010.02.014

Bianchi M, Baulieu EE (2012) 3β-Methoxy-pregnenolone (MAP4343) as an innovative therapeutic approach for depressive disorders. PNAS 109:1713–1718. https://doi.org/10.1073/pnas.1121485109

Borah JM, Chowdhury P (2011) Expedited Baeyer–Villiger oxidation of steroidal ketones by microwave irradiation. Steroids 76:1341–1345. https://doi.org/10.1016/j.steroids.2011.06.014

Borthakur M, Barthakur MG, Boruah RC (2008) Microwave promoted one-pot synthesis of novel A-ring fused steroidal dehydropiperazines. Steroids 73:539–542. https://doi.org/10.1016/j.steroids.2008.01.005

Boruah A, Baruah B, Prajapati D, Sandhu JS (1997) Regeneration of carbonyl compounds from oximes under microwave irradiations. Tetrahedron Lett 38:4267–4268. https://doi.org/10.1016/S0040-4039(97),00875-7

Bryselbout C, Henner P, Lichtfouse E (1998) Fossil fuel biomarkers in plant waxes as pollution parameters. Sci Tot Environ 222(3):201–204. https://doi.org/10.1016/S0048-9697(98)00297-6

Budarin VL, Clark JH, Luque R, Macquarrie DJ (2007) Versatile mesoporous carbonaceous materials for acid catalysis. Chem Commun 6:634–636. https://doi.org/10.1039/b614537j

Bulman Page PC, McCarthy TJ (1991) Oxidation adjacent to C=C Bonds. In: Trost BM, Flemming I (chief eds), Ley SV (vol ed) Comprehensive organic synthesis. Pergammon Press, Oxford.7:83–117. ISBN: 0-08-040598-3

Cichowicz NR, Kaplan W, Khomutnyk Y, Bhattarai B, Sun Z, Nagorny P (2015) Concise enantioselective synthesis of oxygenated steroids via sequential copper(II)-catalyzed michael addition/intramolecular aldol cyclization reactions. J Am Chem Soc 137:14341–14348. https://doi.org/10.1021/jacs.5b08528

Dayal B, Ertel NH (1998) Rapid hydrolysis of bile acid conjugates using microwaves: retention of absolute stereochemistry in the

hydrolysis of (25*R*) 3α,7α,12α- trihydroxy-5β-cholestan-26-oyltaurine. Lipids 33:333–338. https://doi.org/10.1007/s11745-998-0213-y

Dewick PM (2009) The mevalonate and methylerythritol phosphate pathways: terpenoids and steroids. Medicinal natural products: a biosynthetic approach, 3rd edn. Wiley, Chichester, pp 187–310

Djerassi C, Ringgold HJ, Rosenkranz G (1954) Sterodial sapogenins. J Am Chem Soc 76:5533–5536. https://doi.org/10.1021/ja01650a077

Doyle MP, Catino AJ, Choi H, Nichols JM (2012) U S Patent, Patent No. US8, 163:944 B2, April 24

Dsikowitzky L, Schäfer L, Dwiyitno et al (2017) Evidence of massive river pollution in the tropical megacity Jakarta as indicated by faecal steroid occurrence and the seasonal flushing out into the coastal ecosystem. Environ Chem Lett 15:703–708. https://doi.org/10.1007/s10311-017-0641-3

Dunn PJ, Wells AS, Williams MT (eds) (2010) Green chemistry in pharmaceutical industry. Wiley, Weinheim. ISBN 978-3-527-32418-7

Fenyvesi E, Puskás I, Szente L (2018) Applications of steroid drugs entrapped in cyclodextrins. Environ Chem Lett 1:1–2. https://doi.org/10.1007/s10311-018-0807-7

Fernandes P, Cruz A, Angelova B, Pinheriro HM, Cabral JMS (2003) Microbial conversion of steroid compounds: recent developments. Enzym Microb Technol 32:688–705. https://doi.org/10.1016/S0141-0229(03),00029-2

Gogoi S, Shekarrao K, Duarah A, Bora TC, Gogoi S, Boruah RC (2012) A microwave promoted solvent-free approach to steroidal quinolines and their in vitro evaluation for antimicrobial activities. Steroids 77:1438–1445. https://doi.org/10.1016/j.steroids.2012.08.008

Gude VG, Martinez-Guerra E (2018) Green chemistry with process intensification for sustainable biodiesel production. Envirn Chem Lett 16:327–341. https://doi.org/10.1007/s10311-017-0680-9

Gupta P, Mahajan A (2015) Green chemistry approaches as sustainable alternatives to conventional strategies in the pharmaceutical industry. RSC Adv 5:26686–26705. https://doi.org/10.1039/c5ra00358j

Gupta P, Paul S (2014) Solid acids: green alternatives for acid catalysis. Catal Today 236:153–170. https://doi.org/10.1016/j.cattod.2014.04.010

Hegazy MEF, Mohamed TA, EIShamy AI, Mohmed AEIH, Mahalel UA, Reda EH, Shaheen AM, Tawfik WA, Shahat AA, Shams KA, Abdel-Azimm NS, Hammounda FM (2015) Microbial biotransformation as a tool for drug development based on natural products from mevalonic acid pathway: a review. J Adv Res 6:17–33. https://doi.org/10.1016/j.jare.2014.11.009

Hosseinabadi T, Vahidi H, Nickavar B, Kobarfard F (2015) Biotransformation of progesterone by whole cells of Filamentous Fungi *Aspergillus brasiliensis*. Iran J Pharm Res 14:919–924

Huang Y, Zhao D, Liu Chang, Gan C, Zhan J, Lin Q, Shi H, Cui J (2017) Rapid microwave assisted synthesis and antiproliferative evaluation of novel steroidal thiazole derivatives. Chem Res Chin Univ 33:206–212. https://doi.org/10.1007/s40242-017-6372-y

Kakati D, Sarma RK, Saikia R, Barua NC, Sarma JC (2013) Rapid microwave assisted synthesis and antimicrobial bioevaluation of novel steroidal chalcones. Steroids 78:321–326. https://doi.org/10.1016/j.steroids.2012.12.003

Kaplan W, Khatri HR, Nagorny P (2016) Concise enantioselective total synthesis of cardiotonic steroids 19-hydroxysarmentogenin and trewianin aglycone. J Am Chem Soc 138:7194–7198. https://doi.org/10.1021/jacs.6b04029

Khan AT, Ghosh S, Choudhary LH (2005) A highly efficient synthetic protocol for tetrahydropyranylation/depyranylation of alcohols and phenols. Eur J Org Chem 22:4891–4896. https://doi.org/10.1002/ejoc.200500400

LaFrate AL, Gunther JR, Carlson KE, Katzenellenbogen JA (2008) Synthesis and biological evaluation of guanylhydrazone coactivator binding inhibitors for the estrogen receptor. Bioorg Med Chem 16:10075. https://doi.org/10.1016/j.bmc.2008.10.007

Lami L, Casal B, Cuadra L, Merino J, Alvarez A, Ruiz-Hitzky E (1999) Synthesis of 2,4-D ester herbicides: new routes using inorganic solid supports. Green Chem 1:199–204. https://doi.org/10.1039/a902531f

Larsson DG (2014) Pollution from drug manufacturing: review and perspectives. J Philos Trans R Soc B 369:20130571. https://doi.org/10.1098/rstb.2013.0571

Lichtfouse E, Albrecht P (1994) Synthesis of triaromatic steroid hydrocarbons methylated at position 2, 3 or 6: molecular fossils of yet unknown biological origin. Tetrahedron 50(6):1731–1744. https://doi.org/10.1016/S0040-4020(01)80848-6

Lichtfouse E, Riolo J, Albrecht P (1990) Occurrence of 2-methyl, 3-methyl- and 6-methyltriaromatic steroid hydrocarbons in geological samples. Tetrahedron Lett 31(27):3937–3940. https://doi.org/10.1016/S0040-4039(00)97511-7

Lichtfouse E, Albrecht P, Behar F, Hayes JM (1994) A molecular and isotopic study of the organic matter from the Paris basin, France. Geochim Cosmochim Acta 58:209–221. https://doi.org/10.1016/0016-7037(94)90458-8

Lichtfouse E, Leblond C, Da Silva M, Behar F (1998) Occurrence of biomarkers and straight-chain biopolymers in humin: implication for the origin of soil organic matter. Naturwissenschaften 85(10):497–501. https://doi.org/10.1007/s001140050538

Lidstrom P, Tierney J, Wathey B, Westman J (2001) Microwave assisted organic synthesis-a review. Tetrahedron 57:9225–9283. https://doi.org/10.1016/S0040-4020(01),00906-1

Mesquita LMM (2012/2013) Ph.D thesis, University of Coimbra

Misra B, Thakur A, Mahata PP (2015) Pharmaceutical Impurities: a review. IJPC 05:232–239. https://doi.org/10.7439/ijpc.v5i7.2140

Morzycki JW (2011) Application of olefin metathesis in the synthesis of steroids. Steroids 76:949–966. https://doi.org/10.1016/j.steroids.2011.04.002

Orita A, Tanahashi C, Kakuda A, Otera J (2000) Highly efficient and versatile acylation of alcohols with Bi(OTf)(3) as catalyst. Angew Chem Int Ed 39:2877–2879. https://doi.org/10.1002/1521-3773(20000818)39:16%3c2877:AIDANIE2877%3e3.0.CO;2-V

Orita A, Tanahashi C, Kakuda A, Otera J (2001) Highly powerful and practical acylation of alcohols with acid anhydride catalyzed by $Bi(OTf)_3$. J Org Chem 66:8926–8934. https://doi.org/10.1021/jo0107453

Ornelas VP, Cabeza M, Bratoeff E, Heuze I, Sanchez M, Ramirez E, Rodriguez EN (2005) New 5-alpha-reductase inhibitors: in vitro and in vivo effects. Steroids 70:217–224. https://doi.org/10.1016/j.steroids.2004.11.008

Ouyang S, Kuang X, Xu Q, Yin D (2014) Preparation of a carbon based solid acid with high acid density via a novel method. J Mater Sci Chem Eng 2:4–8. https://doi.org/10.4236/msce.2014.26002

Parish EJ, Kizito SA, Qiu Z (2004) Review of chemical syntheses of 7-keto- Δ^5-sterols. Lipids 39:801–804. https://doi.org/10.1007/s11745-004-1299-y

Patel SS, Savjani JK (2015) Systematic review of plant steroids as potential anti-inflammatory agents: current status and future perspectives. JPHYTO 4:121–125

Peterson DH (1985) Autobiography. Steroids 45:1–17. https://doi.org/10.1016/0039-128X(85),90061-3

Salvador JAR, Clark JH (2001) The allylic oxidation of unsaturated steroids by *tert*-butyl hydroperoxide using homogeneous and heterogeneous cobalt acetate. Chem Commun. https://doi.org/10.1039/b007447k

Salvador JAR, Silvestre SM (2005) Bismuth-catalyzed allylic oxidation using t-butyl hydroperoxide. Tetrahedron Lett 46:2581–2584. https://doi.org/10.1016/j.tetlet.2005.02.080

Salvador JAR, Silvestre SM (2006) Processo para a oxidação alílica de compostos insaturados usando hidroperóxido de t-butilo e catalisadores de bismuto, Patente Portuguesa, PT PT Patent 103211B. Patent 103211B

Salvador JAR, Silvestre SM, Moreira VM (2006) Catalytic oxidative processes in steroid chemistry: allylic oxidation, β-selective epoxidation, alcohol oxidation and remote functionalization reactions. Curr Org Chem 10:2227–2257. https://doi.org/10.2174/138527206778742641

Salvador JAR, Silvestre SM, Pinto RMA (2011) Bismuth(III) reagents in steroid and terpene chemistry. Molecules 16:2884–2913. https://doi.org/10.3390/molecules16042884

Salvador JAR, Silvestre SM, Moreira VM (2012) Recent developments in oxidative processes in steroid chemistry. Curr Org Chem 16:1243–1276. https://doi.org/10.2174/138527212800564204

Salvador JAR, Pinto RMA, Silvestre AM (2015) Pharmaceutical green chemistry applied to the chemical synthesis of steroid compounds. Curr Green Chem 2:97–134. https://doi.org/10.2174/2213346101666140915212302

Shan LH, Liu HM, Huang KX, Dai GF, Cao C, Dong RJ (2009) Synthesis of 3β, 7α, 11α-trihydroxy-pregn-21-benzylidene-5-en-20-one derivatives and their cytotoxic activities. Bioorg Med Chem Lett 19:6637–6639. https://doi.org/10.1016/j.bmcl.2009.10.019

Silvestre SM, Silva MMC, Salvador JAR (2016) INTECH, Chap 2, pp 35–56

Smith LL (1984) Steroids. In: Rehm HJ, Reed G, Ebel HF (eds) Biotechnology, a comprehensive treatise in 8 volumes, vol 6a. Verlag-Chemie, Weinheim, pp 31–78

Spinella A, Fortunati T, Soriente A (1997) Microwave accelerated witting reactions of stabilized phosphorus ylides with ketones under solvent free conditions. Synlett 1:93–94. https://doi.org/10.1055/s-1997-689

Stephens JR, Butler PL, Clow CH, Oswald MC, Smith RC, Mohan RS (2003) Bismuth triflate: an efficient catalyst for the formation and deprotection of tetrahydropyranyl ethers. Eur J Org Chem 2003:3827–3831. https://doi.org/10.1002/ejoc.200300295

Swizdor A, Panek A, Milecka-Tronina N, Kolek T (2012) Biotransformations utilizing β-oxidation cycle reactions in the synthesis of natural compounds and medicines. Int J Mol Sci 13:16514–16543. https://doi.org/10.3390/ijms131216514

Tong WY, Dong X (2009) Microbial biotransformation: recent developments on steroid drugs. Recent Pat Biotechnol 3:141–153. https://doi.org/10.2174/187220809788700157

Wendell SG, Edward JP (2016) A short review of methods for the allylic oxidation of Δ^5 steroidal compounds to enones. J Steroids Horm Sci 7:1–5. https://doi.org/10.4172/2157-7536.1000171

Wolfling J (2007) Recent developments in the isolation and synthesis of D-homosteroids and related compounds (LT-2114HR). Arkivoc 5:210–230. https://doi.org/10.3998/ark.5550190.0008.517

Xing R, Liu Y, Wang Y, Chen Li, Wu H, Jiang Y, He M, Wu P (2007) Active solid acid catalysts prepared by sulfonation of carbonization controlled mesoporous carbon materials. Microp Mesop Mater 105:41–48. https://doi.org/10.1016/j.micromeso.2007.06.043

Zhan J, Liu W, Guo H, Zhang Y, Guo D (2003) Selective dehydrogenation of resibufogenin and cinobufagin at 3-OH by *Pseudomonas aeruginosa*. Enzym Microb Technol 33:29–32. https://doi.org/10.1016/S0141-0229(03),00068-1

Zlotos DP (2005) Recent advances in neuromuscular blocking agents. Mini-Rev Med Chem 5:595–606. https://doi.org/10.2174/1389557054023215

Zohri AA, Galil Abdel MSM (1999) Progesterone transformations by three species of Humicola. Folia Microbiol 44:277–282