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p-TsOH-Catalyzed one-pot transformation of di- and trihydroxy steroids towards diverse A/B-ring oxo-functionalization†

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†Electronic Supplementary Information (ESI) available: Natural sources of various ketosteroids; schematic presentations for the earlier laboratory syntheses of various ketosteroids related to this paper; schematic presentations for the bioconversion routes to some ketosteroids; biological reports of some ketosteroids and copies of ^{1}H and ^{13}C NMR spectra of the isolated products. See DOI: 10.1039/x0xx00000x

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Abstract

A solid support-mediated *p*-TsOH-catalyzed milder transformative protocol is developed to furnish diverse ring-A and/or ring-B oxo-functionalized steroids. To flourish interesting isomers involving A/B-ring of the biomolecules in one-pot, only solid-supports (and not solution!) were effective. *p*-TsOH/SiO_2-Oxidation of 4β–hydroxycholesterol, the major oxysterol in human circulation, into a mixture of cholest-4-en-3-one, cholest-4-ene-3,6-dione and 5α-cholestane-3,6-dione was the starting endeavor to further the present scope. The reaction protocol was optimized in detail, and efforts toward the mechanistic understanding favoring the solid support were also evaluated, and a possible synergetic catalytic system involving *p*-TsOH and SiO_2 is expected. Application of the novel methodology to 4β,7α-dihydroxy steroids results the desired diverse

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ketosteroids through oxidation/oxidative dehydration which generalizes the process as a facile multi-oxo-functionalization steroidal transformation.

1. Introduction

Oxysteroids, the steroids having oxygen bearing functionalities, are the major steroid derivatives which owe prime attention both from chemical as well as biological perspective.[1] And among the oxysteroids, different ketosteroids where one or more carbonyl (>C=O) functionality is/are distributed in different steroidal skeletal position, reveal the wide scope of having a variety of biological activities depending on the various isomeric options available. On the other hand, these particular oxysteroids are distributed in nature widely having the basic skeleton of cholesterol or β-sitosterol, for the former is the major *zoo*steroid whereas the latter is the most abundant phytosteroid.

Nature remains the major source of ketosteroids from the very early stages, and especially marine plants and animals are the richest source of them. The major natural ketosteroids of cholesterol and β-sitosterol skeleton[2] are- cholestenone (**1**),[3] stigmastenone (**2**),[3b, 3e,4] cholest-4-ene-3,6-dione (**3**),[3c-3e] stigmast-4,6-dione (**4**),[3c,3d] β-sitost-4-ene-3,6-dione (**16**),[5,6] 5α-cholestane-3,6-dione (**5**),[7] 5α-betasitostane-3,6-dione (**6**),[8-9] cholesta-3,5-diene-7-one (**9**),[3h,10] stigmasta-3,5-diene-7-one (**10**)[11] and cholesta-4,6-diene-3-one (**11**)[3h] (**Fig. 1**). Besides, there are a number of bioactive natural steroids having the similar keto-functionality which do not have the exact cholesterol or β-sitosterol skeleton, *e.g.*, 5α-diones **7** and **8**,[12] and enediones **12** and **13**[13] (**Fig. 1**).

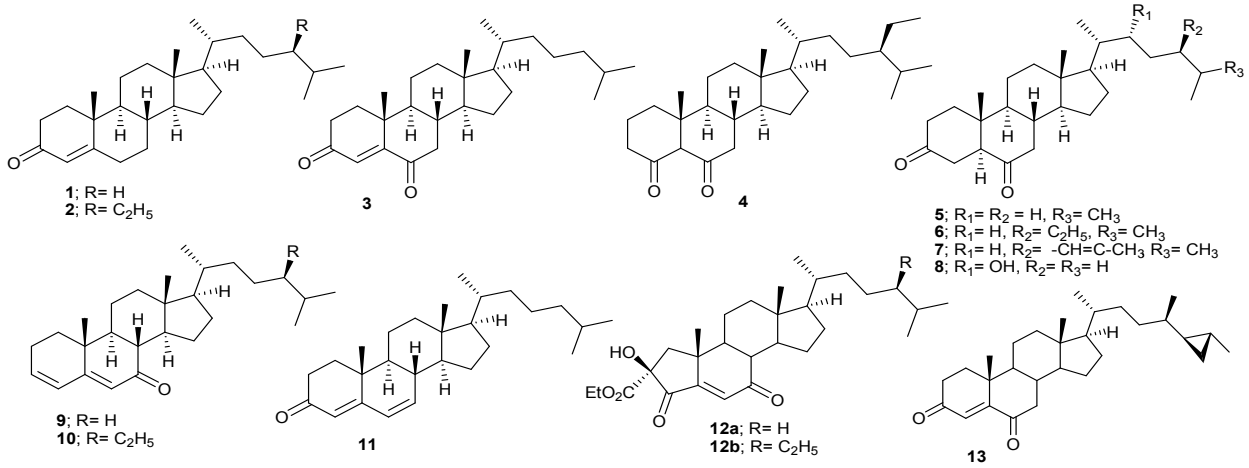

Fig. 1 Natural ketosteroids.

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Besides different biological activities of various ketosteroids,[14] some cholesterol-based derivatives are correlated with their profound and direct implications in human biology. For example, cholestenone (**1**) was found in LDL and VLDL of normal human whereas cholesta-3,5-dien-7-one (**9**) was reported to be present in plasma of normal and diabetic human subjects,[10d] and in normal human liver and alcoholic fatty liver.[10f] It was found also in human atherosclerotic lesions and was found to be a decomposition product of 7-ketocholesterol.[10g] Human gallstones and gallbladder bile also were found to contain cholest-4-en-3-one (**1**), cholesta-4,6-diene-3-one (**11**) and cholesta-3,5-dien-7-one (**9**).[3h] Many of the important steroidal hormones *viz.*, progesterone, testosterone, aldosterone etc., are structurally keto-steroids and in addition, there are a number of marketed drugs, based on various ketosteroid structures, available for various therapeutic applications.[15]

A number of successful syntheses of different ketosteroids are reported earlier. People have utilized different appropriate starting compounds for the syntheses depending upon the scope of the respective transformative reactions. Schematic presentations for the earlier laboratory syntheses of the various ketosteroids related to this paper are provided in section **ES2** in the Electronic Supplementary Information (ESI). These include[16] cholestenone (**1**);[17]; cholest-4-ene-3,6-dione (**3**);[10e,18] 5α-choletane-3,6-dione (**5**);[17b,18a,19] Cholesta-3,5-dien-7-one (**9**);[10e,18a,20] Cholesta-4,6-dien-3-one (**11**)[18b,19b,21] and 5α-Cholestane-4,7-dione (**22**).[22] In addition, a number of conjugated ketosteroids were also found to be the bioconversion products of suitable substrates (please follow section **ES3** in Electronic Supplementary Information, ESI for an schematic presentation).[10e,18r-18t,23]

In analogy to the fact that there are limited attempts of the transformative reactions of natural products with green chemistry concern, none of the reported syntheses of these ketosteroids include the consideration of the green chemistry principles. In this juncture, the present work demonstrates a truly green-steered one-pot transformation to the isomeric ketosteroids, all starting from the highly useful and easily available[24] biomolecules- the dihydroxy- and trihydroxy steroids.

Thus, in brief, considering the significant usefulness of the ketosteroids, on the perspective of potential biological activities, and new synthetic approaches we envisioned to design the present investigation utilizing some oxysteroid biomolecules as the starting materials such as 4β-hydroxy- and 4β,7α-dihydroxy derivatives of cholesterol and β-sitosterol. On the

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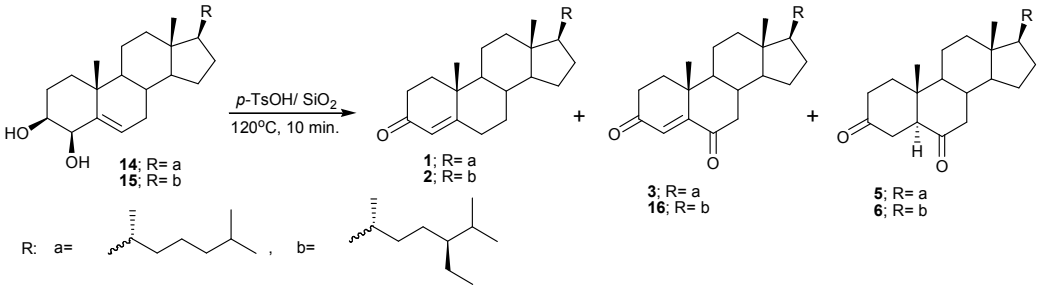
other hand, considering the present day requirement of green chemistry applications, we tried attempting the transformations on solvent-free solid supports which, to our surprise, resulted to achieve in a facile, single-step and greener approach, diverse oxo-functionalized steroids, many of which were interestingly isomeric through the involvement of the ring-A and/ or -B of the steroid skeleton.

2. Results and discussion

In concise, the present work describes the solid support/ *p*-TsOH-catalyzed transformations of 4β-hydroxy- and 4β,7α-dihydroxy derivatives into various (but selective) corresponding ring-A and/ or ring-B ketosteroids (**Scheme 1** and **Scheme 3**). Whereas in solution, the reaction ended up producing a single derivative (please follow captions for **Schemes 1** and **-3**), on the solid supports, 4β-hydroxy steroids yielded the corresponding 4-ene-3-ones, 4-ene-3,6-diones and 5α-3,6-diones; and 4β,7α-dihydroxy steroids produced the corresponding 5-ene-7-ones, -3,5-diene-7-ones, -4,6-diene-3-ones and 5α-4,7-diones (**Schemes 1** and **-3**).



Scheme 1. Solid support- driven steroidal oxo-functionalization: *p*-TsOH/SiO_2 on 4β-hydroxy steroids. In solution phase (in ethanol and dichloromethane) the diols **14** and **15** produce only **1** and **2** respectively. (**1** and **2** were isolated respectively at 64% and 57% yield in DCM; 60% and 56% in ethanol)

2.1 Preparation of the starting materials

The starting materials for the present work, as mentioned above, were- 4β-hydroxy (the diols, **14** and **15**) and 4β,7α-dihydroxy (the triols, **17** and **18**) derivatives of cholesterol and β-sitosterol. These biomolecules were synthesized easily from the respective parent steroids by the oxidation

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with selenium dioxide. The triols were also prepared from the diols after the treatment with same reagent. Detailed syntheses can be found elsewhere.[24]

2.2 Optimization of the reaction conditions

During the test reactions, when 4β-hydroxy cholesterol (**14**) was heated with *p*-TsOH on activated silica, three products isolated were analyzed as cholest-4-en-3-one (**1**), cholest-4-ene-3,6-dione (**3**) and 5α-cholestane-3,6-dione (**5**) (**Scheme 1**). The reaction was attempted in solution phase also using dichloromethane (DCM) and ethanol separately as solvents which yielded, at room temperature (5-10 min.), cholest-4-en-3-one (**1**, 64% and 60% from DCM and ethanol respectively) only and allowing the reaction for longer time (upto 45 min.) did not yield ene-dione **3** and/ or dione **5** at all (by careful TLC experiments). Thus, it was concluded, presumably, that solid silica directed, somehow, the formation of the products **3** and **5**. Then for the preliminary optimization of the reaction conditions we planned to perform the reaction (with *p*-TsOH primarily at 120 mol%) at three different temperatures, *viz.*, at 60^{o}C, 120^{o}C and 180^{o}C using silica gel 60-120 mesh as the reaction medium (**Table 1**; entries 1-3). The reactions at 120^{o}C and 180^{o}C resulted, in a very short time (5-10 minutes), comparable product distribution (**Table 1**, entries 2, 3); whereas at 60^{o}C the reaction took longer time (2 h) for its completion and moreover, cholest-4-ene-3,6-dione (**3**) and 5α-cholestane-3,6-dione (**5**) were produced at lower yields (**Table 1**, entry 1). As our main focus, at this stage, was to emphasize the formation of compounds **3** and **5**, we found it suitable to carry out further optimization reactions at 120^{o}C and 180^{o}C. And considering the anticipated catalytic potentiality of *p*-TsOH,[26] the reactions were carried out taking different amount of the reagent, ranging from 30-240 mol% (**Table 1**, entries 4-9). Analyzing the isolated yields from all the reactions, 60 mol% reagent and 120^{o}C was found to be the optimum reaction condition (**Table 1**, entry 6). Though at 180^{o}C and 60 mol% *p*-TsOH, the yield of the compounds **3** and **5** was little bit higher, the overall conversion was not satisfactory and hence was not chosen as the optimum reaction temperature (**Table 1**, entries 7-8).

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Table 1. Optimization of the reaction conditions taking 4β-hydroxycholesterol (**14**) and *p*-toluenesulfonic acid on activated silica.[a]

Entry	*p*-TsOH (mol%)	Temperature (^{o}C)	Time (min.)	Yield[b] %		
				1	**3**	**5**
1	120	60	120	55	07	06
2	120	120	10	45	08	10
3	120	180	05	41	08	06
4	30	120	10	44	06	04
5	30	180	05	40	08	05
6	**60**	**120**	**10**	**55**	**10**	**10**
7	60	180	05	35	12	10
8	60	180	10	27	13	11
9	240	120	10	44	05	<1

[a]All the reactions were performed on 100 mg (0.248 mmol) of substrate and on 4 g $mmol^{-1}$ of activated silica (60-120 mesh). [b]Isolated pure products by column chromatography.

At the optimized reaction condition, various potential and useful solid supports were then employed as the reaction media (**Table 2**). However, the reaction was first tested without any solid support which furnished only cholestenone **1** at 53% yield and no **3** and **5** at all (**Table 2**, entry 1). Silica gel 60-120 mesh, usually used for the column chromatography produced better result in comparison to silica gel F-254. Both neutral and acidic alumina gave lower yields of compounds **3** and **5**. Montmorillonite KSF, a well applicable clay in the solid phase organic reactions, produced the expected compounds at lower yields in comparison to silica gel 60-120. Ene-dione **3** and dione **5** were not produced at all from 4Å molecular sieves; only cholestenone **1** was isolated at trace amounts.

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Table 2. Optimization of solid supports taking 4β-hydroxycholesterol (**14**) and *p*-TsOH.[a]

Entry	Solid support[b]	Yield[c] %		
		1	**3**	**5**
1	Neat	53	NF	NF
2	**Silica 60-120[d]**	**55**	**10**	**10**
3	Silica F-254	58	05	05
4	Alumina Neutral	40	03	06
5	Alumina acidic	46	02	03
6	Montmorillonite KSF	36	07	07
7	4Å molecular sieves[e]	Traces[f]	NF	NF

[a]All the reactions were performed on 100 mg (0.248 mmol) of substrate (4β-hydroxycholesterol) and 60 mol% of reagent (*p*-TsOH) and for 10 minutes at 120°C. [b]All preactivated solid supports were used at 60 mol% amount. [c] Isolated pure compounds from column chromatography. [d]Under dinitrogen atmosphere the three products were isolated at 62, 5 and 8% of yield respectively. [e]65% of unreacted substrate was recovered. [f]No product was isolated through column chromatography though TLC pointed its formation. NF = not found.

The variation of the amount of silica gel used in the reaction was then performed to observe that whether it can alter the yield distribution. Detailed experiments showed (**Table 3**) that 3g and above of silica gel per mmol of substrate produced comparable yields of the three products.

Table 3. Optimization of the amount of silica 60-120 mesh for the reaction of 4β-hydroxy cholesterol (**14**) with *p*-TsOH.[a]

Entry	Silica (60-120) mesh	Yield[b] %		
		1	**3**	**5**
1	100 mg (0.5 g $mmol^{-1}$)	47	4	3
2	250 mg (1 g $mmol^{-1}$)	50	5	4
3	500 mg (2 g $mmol^{-1}$)	50	5	7
4	750 mg (3 g $mmol^{-1}$)	52	9	10
5	**1g (4 g $mmol^{-1}$)**	**55**	**10**	**10**
6	1.5g (6 g $mmol^{-1}$)	57	7	10

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7	2g (8 gmmol^{-1})	58	7	9

[a]All the reactions were performed on 100 mg (0.248 mmol) of substrate (4β-hydroxycholesterol) and 60 mol% of reagent (*p*-TsOH) and for 10 minutes in 120°C. [b]Isolated pure compounds from column chromatography.

2.3 Mechanistic investigation

After careful examination it was observed that at the same reaction condition silica itself could not react with diol **14**. On the other hand, on activated silica, no appreciable amount of transformation was achieved in glacial acetic acid, and in sulfuric acid; only cholestenone **1** was found to produce along with considerable amount of unreacted diol.[27] The fact implied *p*-TsOH to have some specific role, on the solid surface, towards producing **3** and **5**. Whereas *p*-TsOH (neat, without SiO_2 or other medium, **Table 2**, entry 1) reacted with the diol at the same reaction condition to produce only cholestenone **1** at 53% yield, a separate reaction with *p*-TsOH (60 mol%) along with catalytic amount of silica (50 mol %) induced the formation of **3** and **5** (by TLC). On the other hand, separately in dichloromethane and ethanol, diol **14** was found to be transformed quickly to furnish enone **1** only. These experiments proved a solid support to be an essential medium to achieve the one-pot transformation of the steroidal diol **14** into the enone **1**, endione **3** and dione **5**. Herein, at this point it may be useful to mention that there are a number of reports of different sorbents associated with *p*-TsOH for various useful transformative methodologies.[28]

Applying the optimized reaction condition on cholestenone **1**, it was found important to isolate ene-dione **3** (37%) and dione **5** (32%). Thus it is indeed a two-step process to prepare **3** and **5** in better yields from the diol (*via* **1**). But, when cholestenone **1** itself (without any medium and other reagent) was heated at 120°C for 10 minute neither **3** nor **5** were found to be produced which led us to discard the possibility of aerial oxidation of **1** into **3** and/ or **5**. In addition, it is interesting to mention that when we applied the same reaction condition on ene-dione **3** and dione **5** seperately, no transformation was achieved at all. These results led us to conclude that **3** and **5** were formed only from **1** following two different pathways (**Scheme 2**). This fact was made further convincing by examining the effect of some simple proton scavengers on the reaction (**Table 4**, entries 1-2). This was attempted to reduce the yield of **1** first, which in turn could yield **3** and **5** better if and only if these two were synthesized directly from diol **14** and not

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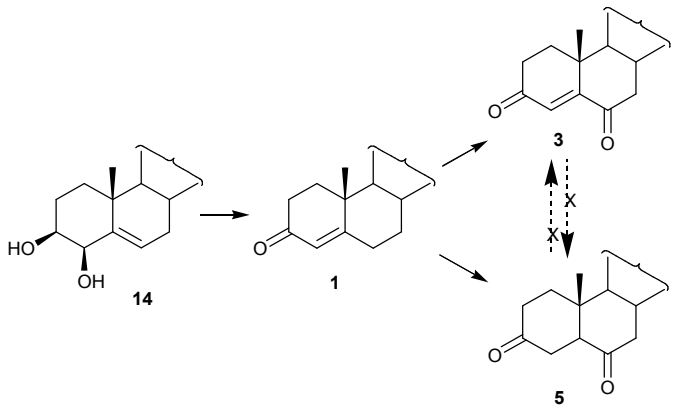
from **1**. The idea was based on the fact that transformation of diol into cholestenone **1** was found to be highly acid sensitive (acid transforms diol **14** rapidly into **1**; also in solution phase and neat) and could occur well in absence of silica. But addition of proton scavengers to the reaction could not affect much the formation of **1** though the yield of **3** and **5** were found to be a little lower. The results altogether thus led silica not to affect the formation of **1** from diol **14** (**Fig. 2**). On the other hand, as the yield of **3** and **5** was not satisfactory as well (in comparison to **1**), and moreover, cholestenone **1** was transformed into **3** and **5** at the same reaction condition. The results thus led to conclude, presumably, that in presence of SiO_2/*p*-TsOH dual system, **3** and **5** were formed only from **1** and not from diol **14** (**Scheme 2**).



Scheme 2. Dienone **3** and dione **5** are formed from **1** following two different routes.

Table 4. Effect of proton scavengers along with *p*-TsOH on the solvent-free transformation of 4β-hydroxy cholesterol.[a]

Entry	Proton scavenger[b]	Yield[c] (%)		
		1	**3**	**5**
1	DMAP[d]	48	5	6
2	Glycine	57	4	7

[a]All the reactions were performed on 100 mg (0.248 mmol) of substrate (4β-hydroxy cholesterol) and 60 mol% of reagent (*p*-TsOH) and for 10 minutes in 120°C taking 1g (4g $mmol^{-1}$) of activated silica 60-120 as the solid support. [b]For each reaction equimolar amount (to *p*-TsOH, i. e., 60 mol%) of proton scavengers were employed. [c]Isolated pure products by column chromatography. [d] *N*, *N*-dimethyl-4-aminopyridine.

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Yamamoto et al., in their informative review flourished the concept of 'designer acids' through the combination of a Brønsted acid with a Lewis acid where one can synergistically affect the other.[29] As such acid combinations were found to produce satisfactory results in the solution phases, and there is no report of any such designer acid working on the solid phase, we thought to examine the concept in our solvent-free ketosteroid syntheses reactions. Thus, we tried the transformation of diol **14** accomplished by *p*-TsOH/SiO_2, separately in presence of $MgCl_2$, $ZnCl_2$ and anhydrous $FeCl_3$. But for the present solid supported transformation, the 'designer acids' concept was remained ineffective as the reactions conducted along with Lewis acids produced almost comparable yield of the three products to the reactions that did not use Lewis acids (**Table 5**, entry 1-3).

Table 5. Effect of Lewis acids along with *p*-TsOH on the solvent-free transformation of 4β-hydroxy cholesterol.[a]

Entry	Lewis acid[b]	Yield[c] (%)		
		1	**3**	**5**
1	$MgCl_2$. $6H_2O$	48	7	7
2	$ZnCl_2$ (anh.)	55	8	10
3	$FeCl_3$ (anh.)	52	10	7

[a]All the reactions were performed on 100 mg (0.248 mmol) of substrate (4β-hydroxy cholesterol) and 60 mol% of reagent (*p*-TsOH) and for 10 minutes in 120°C taking 1g (4g $mmol^{-1}$) of activated silica 60-120 as the solid support. [b]For each reaction equimolar amount (to *p*-TsOH, i. e., 60 mol%) of Lewis acids were employed. [c]Isolated pure products by column chromatography.

There are a number of well enriched reviews describing the excellent scope of silica as a reaction-promoting component, and the usefulness is flourished, moreover through the understanding of their mechanism of action.[30] Opening of an S2R defect in silica with water (**Fig. 3a**)[30f-30h] as well as the cleavage of highly covalent Si-O bonds, either homolytically or heterolytically, lead to the major physicochemical processes on silica surfaces.[30h-30k]

Out of the various species generated *in situ* due to the breakage of Si-O bonds, silyl (both $\equiv Si^{\bullet}$ and $\equiv Si^{+}$) and siloxy (both $\equiv Si-O^{\bullet}$ and $\equiv Si-O^{-}$) species owe to be the best suitable surface sites in describing the mechanism for the present reaction (cationic-anionic cleavage is

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shown in **Fig. 3b**).[30h,30i] Thus we believe that the pathway for the formation of **3** and **5**, from **1** utilizes the surface composing silyl cation countered with *p*-toluenesulphonyl anion, and siloxy anion countered with proton (the reaction medium is acidic!). And the modified composition renders to be the better couple of solid support/acid possibly due to $^{-}\overset{|}{\underset{|}{Si}}^{+}\ ^{-}OTs$, and as the other combinations were ineffective, there exists a possibility of synergetic catalysis of *p*-TsOH with SiO_2 towards analyzing the products which were only due to the solid supports.

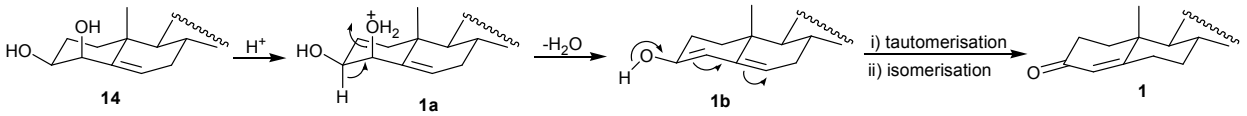

Figure 2. Acid-catalyzed transformation of 4β-hydroxycholesterol (**14**) into cholest-4-en-3-one, **1**. Solid silica probably does not affect the formation of **1**.

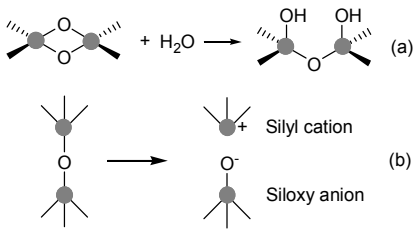

Figure 3. (a) Opening of an S2R defect in silica with water. (b) One of the probable silica surface sites due to cleavage. (● = Si)

2.4 Application of the reaction protocol on different polyhydroxy steroids

The optimized reaction condition was then applied to other comparable steroidal biomolecules. To generalize the reaction methodology the di-/tri-hydroxy steroids chosen were the 4β-hydroxy derivatives of β-sitosterol (**15)** and 4β,7α-dihydroxy derivatives of cholesterol and β-sitosterol (**17** and **18** respectively).

When 4β-hydroxy β-sitosterol (**15**) was treated with 60 mol% of *p*-TsOH on activated silica (60-120 mesh) at 120°C for 10 min, stigmastenone (**2,** 42%), stigmast-4-en-3,6-dione (**16**, 10%) and 5α-stigmastane-3,6-dione (**6**, 8%) were isolated as pure products (**Scheme 1**). Of note, in analogy to the results found with the diol, when the reaction was attempted with 4β,7α-dihydroxycholesterol (**17**) in solution taking dichloromethane as the solvent, cholesta-4,6-dien-3-one (**11**, 54%) was found to be the only product formed (this route is, thus, found easily useful to

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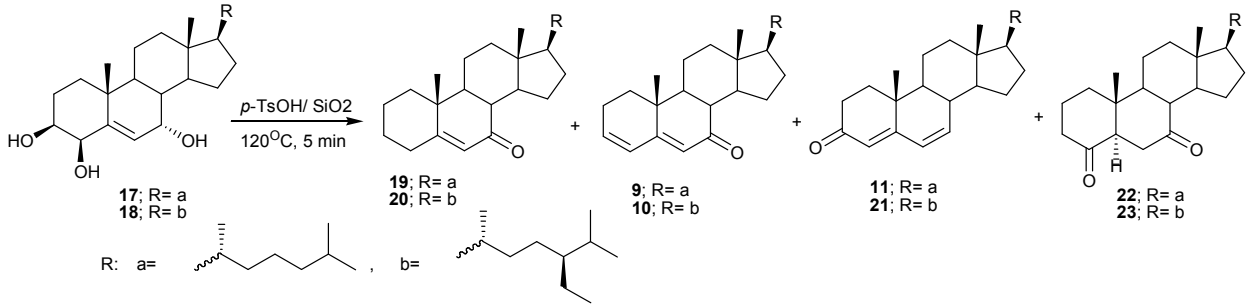
synthesize dienone **11** from cholesterol *via* triol **17**). On the other hand, on solid silica, the same reaction condition applied to this triol **17** furnished four different ketosteroids: i) cholest-5-en-7-one (**19**, 8%), ii) cholesta-3,5-dien-7-one (**9**, 13%), iii) cholesta-4,6-dien-3-one (**11**, 17%) and iv) 5α-cholestane-4,7-dione (**22**, 7%). In the ketocholesterol series, the products, overall, thus led to achieve interesting isomeric pairs, such as **9** and **11**; **19** and **1**; **22** and **5** (**Schemes 1** and **-3**)**.** Accordingly, four keto-functionalized derivatives of the phytosteroid β-sitosterol were isolated by employing the reaction on 4β,7α-dihydroxy β-sitosterol (**18**): i) stigmast-5-en-7-one (**20**, 10%), ii) stigmasta-3,5-dien-7-one (**10**, 18%), iii) stigmasta-4,6-dien-3-one (**21**, 17%) and iv) 5α-stigmastane-4,7-dione (**23**) (**Scheme 3**); but compound **23** could not be isolated in pure form. It was obtained as a non-separable mixture with other enones and dienononones (by NMR). However, like the cholesterol analogues, here also the isolated compounds correspond overall to the interesting isomeric pairs in the keto-β-sitosterol series, such as **20** and **2**; **10** and **21**; **23** and **6** (**Schemes 1** and **-3**). In this context it is interesting to note that the reaction protocol, though in general, furnished the oxosteroids both from the steroidal diols and triols, the reaction outcome is different. In the same reaction condition, whereas the diols yield the corresponding oxo-derivatives by following only oxidation, the triols undergo simultaneous oxidation as well as reduction (or, oxidative dehydration; *e.g.*, **17** to **19**) to result the corresponding oxosteroids, and this difference in reactivity is attributed due to the 7α-hydroxy group in triol which renders an additional dehydration site towards more possible intermediate/s suitable for reduction/ oxidative dehydration.



Scheme 3. Solid support-driven steroidal oxo-functionalization: *p*-TsOH/SiO_2 on 4β,7α-dihydroxy steroids. In solution phase (in dichloromethane) the triol **17** produced only **11** (54% isolated yield).

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3. Conclusion

In summary, a solid support/*p*-TsOH-catalyzed milder, facile and greener transformative procedure to yield ring-A and/or ring-B oxo-functionalized steroids has been accomplished. Whereas in the solution phase, the di- and trihydroxy steroids were found to result a single product in each case, solid supports interestingly induced the formation of various other (but selective) ketosteroids which altogether furnished a group of practically useful isomeric pairs in the respective ketosteroid series. Detailed optimization of the reaction conditions along with the modest experiments involving SiO_2/*p*-TsOH dual system to understand the mechanism lead presumably towards a possibility of a synergistic catalysis of *p*-TsOH with SiO_2 for analyzing the products which were only due to the solid supports.

4. Experimental

4.1 General

Melting points were measured in open capillary methods and were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on BruckerAvance 300MHz FT-NMR spectrometer using 5 mm BBO probe. $CDCl_3$ was used as solvent and TMS as reference material. Data are presented as follows: chemical shift in ppm on the scale relative to $\delta_{TMS} = 0$; coupling constant in *J*/Hz. Infrared spectra were recorded either on Shimudzu FT-IR 8300 Spectrometer or Perkin Elmer FT-IR Spectrometer *Spectrum RX 1* as neat or thin films (KBr or Nujol) as indicated in the experimental procedures, and at room temperature. Frequencies are given in wave numbers (cm^{-1}). For column chromatography silica gel G, 60-120 mesh was used with petroleum ether-ethyl acetate mixture as the eluent. For thin layer chromatography (TLC), freshly made silica gel plates (using silica gel for TLC + petroleum ether) were used and visualization was achieved by staining with iodine.

4.2 General reaction of compounds 14, 15, 17 and 18 for the syntheses of the respective ketosteroids

4β-Hydroxycholesterol (**14**, 100 mg, 0.25 mmol) and a given amount of *p*-toluenesulfonic acid (please follow **Table 1**) were mixed homogenously with the pre-activated (150^{o}C/1 mm Hg, 1h) solid support (1g) in a dry mortar to dust by a pestle, transferred into a round bottomed flask (50 mL). The mixture was then heated in an oil bath at defined temperature for specific time. The

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reaction mixture was cooled, water (10 mL) was poured into it and the organic materials were extracted in diethyl ether, washed with water (3× 15 mL) and the organic extract was dried (Na_2SO_4) and the solvent was removed (vacuum). The residue was then subjected to silica gel column chromatography to separate the products: cholestenone (**1**, from 5% ethyl acetate/ pet ether, starting fractions), cholest-4-ene-3,6-dione (**3,** from 5% ethyl acetate/ pet ether, latter fractions) and 5α-cholestane-3,6-dione (**5**, from 8% ethyl acetate/ pet ether). General reaction procedure of compounds **15**, **17** and **18** to furnish the respective ketosteroids are completely same with that of diol **14**.

4.3 Product characterization

Cholestenone (1): Eluent in column chromatography: 5% ethyl acetate in petroleum ether. Yield: trace-58%. Pale yellow crystal. m.p. 78-79^oC (methanol). ^1H NMR (300 MHz, $CDCl_3$): δ 0.71 (s, 3H, Me-18), 0.85 (d, *J*=1.5 Hz, 3H, Me-27), 0.88 (d, *J*=1.5 Hz, 3H, Me-26), 0.91 (d, *J*=6.6 Hz, 3H, Me-21), 1.18 (s, 3H, Me-19), 2.03 (dd, *J*=13.2 Hz and 3.3 Hz, 1H, H-2), 2.29-2.44 (m, 1H, H-2), 5.73 (s, 1H, H-4). ^{13}C NMR: (75 MHz, $CDCl_3$): δ 11.89 (CH_3-18), 17.51(CH_3-19), 18.65 (CH_3-21), 21.00 (CH_2-11), 22.56 (CH_3-26), 22.83 (CH_3- 27), 23.79 (CH_2-15), 24.17 (CH_2-23), 28.00 (CH_2-25) 28.17 (CH_2-16), 32.02 (CH_2-22), 32.95 (CH_2-6), 35.58 (CH_2-1), 35.66 (CH_2-2), 35.74 (CH-20), 36.06 (CH-8), 38.58 (CH_2-7), 39.47 (CH_2-24), 39.47 (CH_2-12), 39.59 (C-10), 42.36 (C-13), 53.78 (CH-9), 55.84 (CH-17), 56.06 (CH-14), 123.71 (CH-4), 171.80 (C-5), 199.74 (C-3). FTIR (nujol, cm^{-1}): ν 2345, 1684, 1654, 1618, 1560, 1508, 1377, 1266, 1227, 868.09, 722.

Cholest-4-en-3,6-dione (3): Eluent in column chromatography: 5% ethyl acetate in petroleum ether. Yield: 5-13%. pale yellow crystal. m.p. 124-125^oC (methanol). ^1H NMR (300 MHz, $CDCl_3$): δ 0.72 (s, 3H, Me-19), 0.86 (s, 3H, Me-27), 0.88 (s, 3H, Me-26), 0.93 (d, *J*=6.6Hz, 3H, Me-21), 1.17 (s, 3H, Me-18), 2.49-2.55 (m, 3H, H-2 and H-7), 2.63 (dd, *J*=15.9Hz and 3.9Hz, 1H, H-2 or H-7), 6.17 (s, 1H, H-4). ^{13}C NMR: (75 MHz, $CDCl_3$): δ 11.89 (CH_3-18), 17.51 (CH_3-19), 18.65 (CH_3-21), 20.88 (CH_2-11), 22.56 (CH_3-26), 22.81 (CH_3- 27), 23.79 (CH_2-15), 23.97 (CH_2-23), 28.01 (CH_2-25) 28.01 (CH_2-16), 33.98 (CH_2-1), 34.22 (CH_2-22), 35.54 (CH_2-2), 35.68 (CH-20), 36.06 (CH-8), 39.14 (CH_2-24), 39.46 (CH_2-12), 39.82 (C-10), 42.54 (C-13), 46.83 (CH_2-7), 50.99 (CH-9), 55.96 (CH-17), 56.56 (CH-14), 125.45 (CH-4), 161.11 (C-5), 199.55

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(CH_2-6), 202.38 (C-3). FTIR (nujol, cm^{-1}): ν 2345, 1686, 1654, 1560, 1542, 1508, 1376, 1222. Analysis calcd: C, 81.35; H, 10.62. Found: C, 81.15; H, 10.82.

5α-Cholestane-3,6-dione (5): Eluent in column chromatography: 10% ethyl acetate in petroleum ether. Yield: trace-11%. pale yellow crystal. m.p. 170-173°C (acetone). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.69 (s, 3H, Me-18), 0.86 (s, 3H, Me-27), 0.88 (s, 3H, Me-26), 0.92 (d, *J*=6.3Hz, 3H, Me-21), 0.96 (s, 3H, Me-19), 2.30-2.50 (m, 5H, H-4, H-5, H-7), 2.54-2.61 (m, 2H, H-2). ^{13}C NMR: (75 MHz, $CDCl_3$): δ 12.01 (CH_3-18), 12.57 (CH_3-19), 18.62 (CH_3-21), 21.66 (CH_2-11), 22.55 (CH_3-26), 22.82 (CH_3- 27), 23.79 (CH_2-15), 23.99 (CH_2-23), 28.00 (CH_2-25) 28.00 (CH_2-16), 35.68 (CH-20), 36.04 (CH_2-22), 37.00 (CH_2-1), 37.40 (CH_2-2), 38.03 (CH-8), 38.08 (CH-4), 39.35 (CH_2-24), 39.44 (CH_2-12), 41.26 (C-10), 42.99 (C-13), 46.63 (CH_2-7), 53.43 (CH-9), 56.07 (CH-17), 56.66 (CH-14), 57.49 (C-5), 209.27 (CH_2-6), 211.44 (C-3). FTIR (nujol, cm^{-1}): ν 1717, 1654, 1560, 1376. Analysis calcd: C, 80.94; H, 11.07. Found: C, 81.15; H, 11.17.

Stigmastenone (2): Eluent in column chromatography: 3% ethyl acetate in petroleum ether. Yield: 42%. pale yellow crystal. m.p. 93-94°C (acetone-methanol).^{1}H NMR (300 MHz, $CDCl_3$): δ 0.72 (s, 3H, Me-18), 0.80 (s, 3H, Me-27), 0.84 (d, J=6.3Hz, 3H, Me-26), 0.87 (s, 3H, Me-29), 0.92 (d, *J*=6.6 Hz, 3H, Me-21),1.18 (s, 3H, Me-19), 2.03 (dd, *J*=19.8 Hz and 3.3Hz, 1H, H-2), 2.29-2.47 (m, 1H, H-2), 5.73 (br s, 1H, H-4). ^{13}C NMR: (75 MHz, $CDCl_3$): δ 12.01 (CH_3-18), 12.01 (CH_3-29), 17.45 (CH_3-26), 18.76 (CH_3-21), 19.01 (CH_3-19), 19.83 (CH_3- 27), 21.11 (CH_2-11), 23.18 (CH_2-28), 24.24 (CH_2-15), 26.28 (CH_2-25) 28.22 (CH_2-16), 29.31 (CH_2-23), 32.14 (CH_2-2), 33.00 (CH_2-6), 34.02 (CH_2-22), 34.02 (CH_2-7), 35.78 (CH_2-1), 35.78 (CH-8), 36.17 (CH-20), 38.67 (C-10), 39.73 (CH_2-12), 42.48 (C-13), 45.96 (CH_2-24), 53.92 (CH-9), 55.98 (CH-17), 56.14 (CH-14), 123.80 (CH-4), 171.56 (C-5), 199.51 (C-3). FTIR (nujol, cm^{-1}): ν 2345, 1683, 1618, 1560, 1542, 1508, 1377, 1267, 1227, 1186, 958, 866, 722.

Stigmast-4-en-3,6-dione (16): Eluent in column chromatography: 3% ethyl acetate in petroleum ether. Yield: 10%. pale yellow crystal. m.p. 151-152°C (chloroform-methanol). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.72 (s, 3H, Me-18), 0.81 (s, 3H, Me-27), 0.83 (s, 3H, Me-26), 0.85 (s, 3H, Me-29), 0.94 (d, *J*=6.3Hz, 3H, Me-21), 1.17 (s, 3H, Me-19), 2.04 (d, *J*=3.0Hz, 1H, H-7), 2.47-2.55

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(m, 2H, H-2), 2.68 (dd, *J*=15.6Hz and 3.9Hz, 1H, H-7), 6.17 (br s, 1H, H-4). ^{13}C NMR: (75 MHz, $CDCl_3$): δ 11.88 (CH_3-18), 11.96 (CH_3-29), 17.50 (CH_3-19), 18.69 (CH_3-21), 18.99 (CH_3-26), 19.83 (CH_3- 27), 20.85 (CH_2-11), 23.02 (CH_2-28), 23.96 (CH_2-15), 25.95 (CH_2-23), 28.01 (CH_2-16), 29.07 (CH_2-25), 33.79 (CH_2-22), 33.97 (CH_2-2), 34.19 (CH-8), 35.50 (CH_2-1), 36.03 (CH-20), 39.09 (CH_2-12), 39.82 (C-10), 42.51 (C-13), 45.75 (CH_2-24), 46.83 (CH_2-7), 50.94 (CH-9), 55.80 (CH-17), 56.51 (CH-14), 125.44 (CH-4), 161.12 (C-5), 199.61 (C-3), 202.46 (CH_2-6). FTIR (nujol, cm^{-1}): ν 2345, 1686, 1654, 1618, 1560, 1542, 1508, 1376, 1222. Analysis calcd: C, 81.63; H, 10.87. Found: C, 81.41; H, 10.62.

5α-Stigmastane-3,6-dione (6): Eluent in column chromatography: 8% ethyl acetate in petroleum ether. Yield: 8%. pale yellow crystal. m.p. 192-194^{o}C (acetone). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.69 (s, 3H, Me-18), 0.81 (s, 3H, Me-27), 0.83 (s, 3H, Me-29), 0.85 (s, 3H, Me-26), 0.93 (d, *J*=6.3Hz, 3H, Me-21), 0.96 (s, 3H, Me-19), 2.25-2.45 (m, 5H, H-4, H-5, H-7), 2.54-2.61 (m, 2H, H-2). ^{13}C NMR: (75 MHz, $CDCl_3$): δ 11.96 (CH_3-18), 12.01 (CH_3-29), 12.56 (CH_3-19), 18.66 (CH_3-21), 18.99 (CH_3-26), 19.83 (CH_3- 27), 21.66 (CH_2-11), 23.02 (CH_2-28), 24.00 (CH_2-15), 25.96 (CH_2-23), 28.05 (CH_2-16), 29.06 (CH_2-25) 33.78 (CH_2-22), 36.04 (CH-20), 37.00 (CH-4), 37.40 (CH_2-2), 38.03 (CH-8), 38.08 (CH_2-1), 39.34 (CH_2-12), 41.27 (C-10), 42.99 (C-13), 45.75 (CH_2-24), 46.63 (CH_2-7), 53.43 (CH-9), 55.97 (CH-17), 56.58 (CH-14), 57.50 (C-5), 209.28 (CH_2-6), 211.47 (C-3). FTIR (nujol, cm^{-1}): ν 1707, 1685, 1618, 1560, 1542, 1508, 1377, 1260, 1239. Analysis calcd: C, 81.25; H, 11. 29. Found: C, 81.05; H, 11.02.

Cholest-5-en-7-one (19): Eluent in column chromatography: 2% ethyl acetate in petroleum ether. Yield: 8%. pale yellow gum. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.71 (s, 3H, Me-19), 0.72 (d, *J*=7.2 Hz, 3H, Me-27), 0.82 (d, *J*=6.3 Hz, 3H, Me-26), 0.91(d, *J*=6.6 Hz, 3H, Me-21), 1.13 (s, 3H, Me-18), 3.08 (d, *J*=7.2 Hz, 1H, H-8), 6.07 (s, 1H, H-6). ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.97, 17.15, 18.68, 20.99, 22.56, 22.82, 23.09, 23.83, 24.24, 28.02, 28.21, 31.05, 31.81, 34.68, 35.23, 35.77, 36.15, 37.80, 39.52, 39.72, 42.38, 54.27, 56.03, 56.17, 140.46, 141.13, 193.67. FTIR (nujol, cm^{-1}): ν 1684.

Cholesta-3,5-dien-7-one (9): Eluent in column chromatography: 2% ethyl acetate in petroleum ether. Yield: 13%. pale yellow crystal. m.p. 112-114^{o}C (ethanol).^{1}H NMR (300 MHz, $CDCl_3$): δ

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0.69 (s, 3H, Me-18), 0.86 (s, 3H, Me-27), 0.88 (s, 3H, Me-26), 0.92 (d, *J*=6.6 Hz, 3H, Me-21), 1.09 (s, 3H, Me-19), 6.11 (dd, *J*=9.9 Hz and 3.0 Hz, 1H, H-4), 6.80 (q, *J*=2.4 Hz, H-6) (for 19 Me), 6.89 (ddd, *J*=10.2 Hz, 6.3 z and 2.4 Hz, 1H, H-3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.92, 18.75, 21.04, 21.41, 22.57, 22.82, 23.85, 24.17, 28.03, 28.19, 31.26, 31.93, 35.77, 38.62, 36.19, 39.32, 39.53, 39.58, 42.39, 49.44, 56.15, 56.56, 129.19, 134.81, 141.74, 147.63, 188.48. FTIR (nujol, cm^{-1}): ν 1677, 1635, 1619, 1560, 1542, 1377, 1301, 1265, 1150, 1078, 1021, 960, 891, 849, 815, 723, 670. Analysis calcd: C, 84.75; H, 11.06. Found: C, 84.55; H, 11.22.

Cholesta-4,6-diene-3-one (11): Eluent in column chromatography: 5% ethyl acetate in petroleum ether. Yield: 17%. pale yellow crystal, m.p. 80-81^{o}C (methanol). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.76 (s, 3H, Me-18), 0.86 (d, *J*=1.2 Hz, 3H, Me-26), 0.89 (d, *J*=1.2 Hz, 3H, Me-29), 0.93 (d, *J*=6.6 Hz, 3H, Me-21), 1.12 (s, 3H, Me-19), 5.67 (s, 1H, H-4), 6.12 (ddd, *J*= 1.8 Hz, 18 Hz and 9.9 Hz, 2H, H-6 and H-7). ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.93, 16.32, 18.70, 20.74, 22.56, 22.80, 23.77, 23.90, 28.03, 28.18, 34.00 (2), 35.81, 36.14, 36.19, 37.83, 39.54, 39.65, 43.49, 50.80, 53.53, 56.14, 123.55, 127.82, 141.56, 164.01, 199.55. FTIR (nujol, cm^{-1}): ν 1688. Analysis calcd: C, 84.75; H, 11.06. Found: C, 84.65; H, 10.92.

Cholest-4,7-dione (22): Eluent in column chromatography: 5% ethyl acetate in petroleum ether. Yield: 7%. pale yellow crystal, m.p. 144-146^{o}C (chloroform-methanol). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.66 (s, 3H, Me-18), 0.85 (d, *J*=1.2 Hz, 3H, Me-27), 0.87 (d, *J*= 1.2 Hz, 3H, Me-26), 0.91 (d, *J*=6.3 Hz, 3H, Me-21), 1.01 (s, 3H, Me-19), 2.25-2.35 (m, 3H), 2.52-2.54 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.09, 13.21, 18.81, 22.05, 22.80, 22.56, 23.81, 24.89, 28.02, 28.40, 29.71, 35.65, 36.17, 37.17, 38.74, 38.94, 39.49, 40.95, 42.44, 42.79, 48.86, 49.56, 55.12, 55.95, 59.89, 209.58, 212.52. FTIR (nujol, cm^{-1}): ν 1719, 1705, 1653, 1376, 1270, 1154, 751, 721, 667. Analysis calcd: C, 80.94; H, 11.07. Found: C, 85.11; H, 11.02.

Stigmast-5-en-7-one (20): Eluent in column chromatography: 2% ethyl acetate in petroleum ether. Yield: 10%. pale yellow gum. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.71 (s, 3H, Me-18), 0.80 (s, 3H, Me-27), 0.84 (d, *J*=6.3 Hz, 3H, Me-26), 0.87(s, 3H, Me-29), 0.92 (d, *J*=6.3 Hz, 3H, Me-21), 1.17 (s, 3H, Me-19), 6.07 (s, 1H, H-6). ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.99, 17.16, 18.75, 19.06, 19.83, 21.00, 23.12, 24.25, 26.15, 28.24, 29.22, 29.71, 31.07, 31.82, 33.94, 34.69, 35.26,

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37.81, 36.15, 39.73, 42.40, 45.89, 54.28, 56.04, 140.46, 141.14, 193.66. FTIR (nujol, cm^{-1}): ν 1686. Analysis calcd: C, 84.40; H, 11.72. Found: C, 84.64; H, 11.82.

Stigmasta-3,5-diene-7-one (10): Eluent in column chromatography: 2% ethyl acetate in petroleum ether. Yield: 18%. pale yellow solid, m.p. 122°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.70 (s, 3H, Me-18), 0.79 (s, 3H, Me-27), 0.84 (d, *J*=6.6 Hz, 3H, Me-26), 0.88 (s, 3H, Me-29), 0.94 (d, *J*=6.6 Hz, 3H, Me-21), 1.09 (s, 3H, Me-19), 2.06 (dt, *J*=6.0 Hz and 3.3 Hz, 1H, H-2),2. 32 (t, *J*= 5.4 Hz, 1H, H-8), 2.45 (dd, *J*= 19.8 Hz and 6.3 Hz, 1H, H-2), 6.11 (dd, *J*=9.9 Hz and 2.7 Hz, 1H, H-4), 6.80 (q, *J*=2.7 Hz, 1H, H-6) (for 19 Me), 6.88 (ddd, *J*=9.9 Hz, 6.3 Hz and 2.4 Hz, 1H, H-3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.92, 12.01, 18.81, 19.07, 19.83, 21.04, 21.40, 23.13, 24.18, 26.17, 28.21, 29.22, 31.26, 31.93, 33.98, 36.14, 38.62, 39.32, 39.58, 42.39, 45.90, 49.44, 56.06, 56.56, 129.19, 134.81, 141.74, 147.63, 188.47. FTIR (nujol, cm^{-1}): ν 1670, 1654, 1630, 1617, 1560, 1377, 1274, 1155, 960, 783, 722. Analysis calcd: C, 84.81; H, 11.29. Found: C, 84.65; H, 11.02.

Stigmasta-4,6-diene-3-one (21): Eluent in column chromatography: 5% ethyl acetate in petroleum ether. Yield: 17%. pale yellow crystal, m.p. 66-70°C (methanol). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.76 (s, 3H, Me-18), 0.82 (d, *J*=6.3 Hz, 3H, Me-26), 0.87 (d, *J*=7.2 Hz, 3H, Me-29), 0.93 (d, *J*=6.3 Hz, 3H, Me-21), 1.11 (s, 3H, Me-19), 5.66 (s, 1H, H-4), 6.12 (ddd, *J*= 1.8 Hz, 18 Hz and 9.1 Hz, 2H, H-6 and H-7). ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.92, 12.01, 16.32, 18.75, 19.08, 19.83, 20.72, 23.14, 23.77, 27.12, 28.21, 29.26, 29.53, 33.98, 33.98, 36.13, 37.14, 37.81, 39.62, 43.47, 50.77, 45.92, 53.51, 56.02, 123.53, 127.80, 141.61, 164.06, 199.63. FTIR (nujol, cm^{-1}): ν 1687. Analysis calcd: C, 84.81; H, 11.29. Found: C, 84.55; H, 11.09.

5α-Stigmastane-4,7-dione (**23,** as mixture**):** Eluent in column chromatography: 5% ethyl acetate in petroleum ether. From NMR spectral data of the non-seperable mixture of the titled compound with other enones and dienones, only the values correspond to 5α-stigmastane-4,7-dione (obtained with the help of the spectral values of the corresponding pure 5α-cholestane-4,7-dione, **22**) are produced here. The δ values, especially for ^{13}C, as collected from a mixture of a number of peaks, may be little bit different for the actual pure compound. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.66 (s, 3H, Me-18), 0.84 (d, *J*=6.0 Hz, 3H, Me-27), 0.88 (d, *J*= 2.7 Hz, 3H, Me-26), 0.92 (d,

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J=6.3 Hz, 3H, Me-21), 1.01 (s, 3H, Me-19). ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.94, 12.01, 13.20, 14.10, 18.8, 21.83, 22.53, 22.70, 23.15, 24.91, 28.21, 28.42, 36.14, 37.19, 38.75, 38.95, 39.59, 40.94, 42.44, 42.79, 45.45, 48.88, 49.40, 49.60, 55.04, 55.96, 59.91, 209.54, 212.50.

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2 Please follow section ES1 in the electronic supplementary information (ESI) for the exact natural sources of these ketosteroids.

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14 Please follow section **ES4** in the electronic supplementary information (ESI) for a brief biological evaluation of some selective ketosteroids related to this paper.

15 To name few of the ketosteroid-based marketed drugs: exemestane, medrogestone, prednisone, dutasteride.

16 The references associated with the respective compounds are only due to their syntheses.

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A milder, facile and greener transformative protocol, specific on solid supports, to yield ring-A and/or ring-B oxo-functionalized steroids has been accomplished.