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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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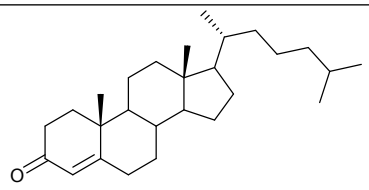
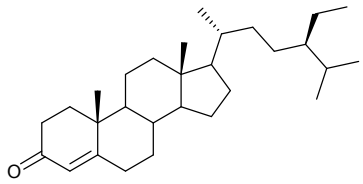
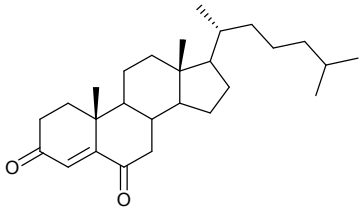
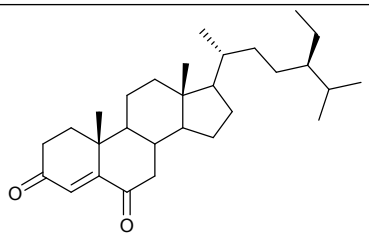
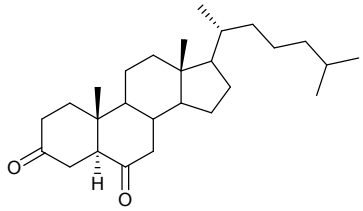
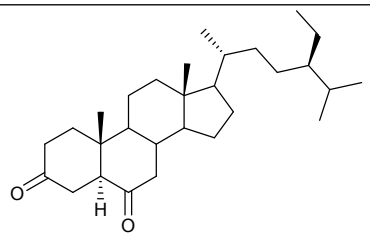
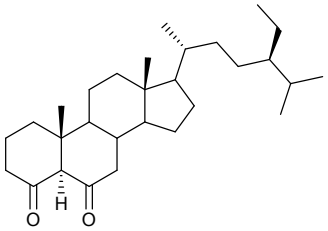
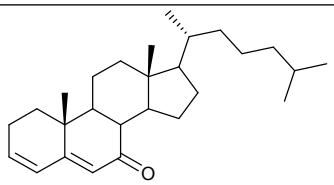
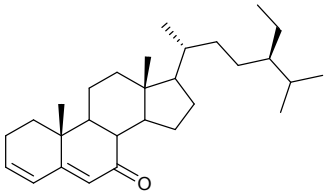
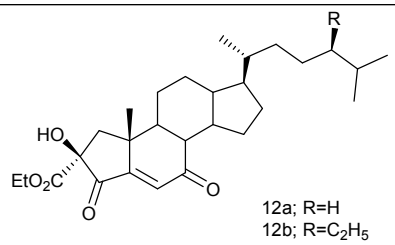
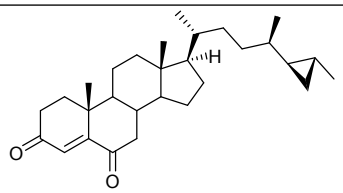
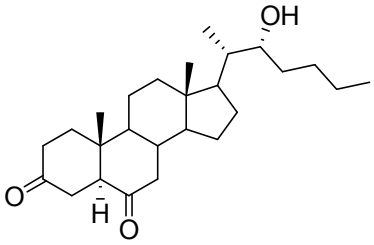
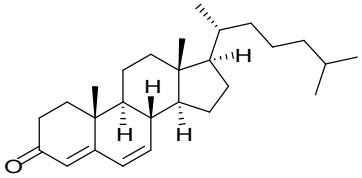
Contents

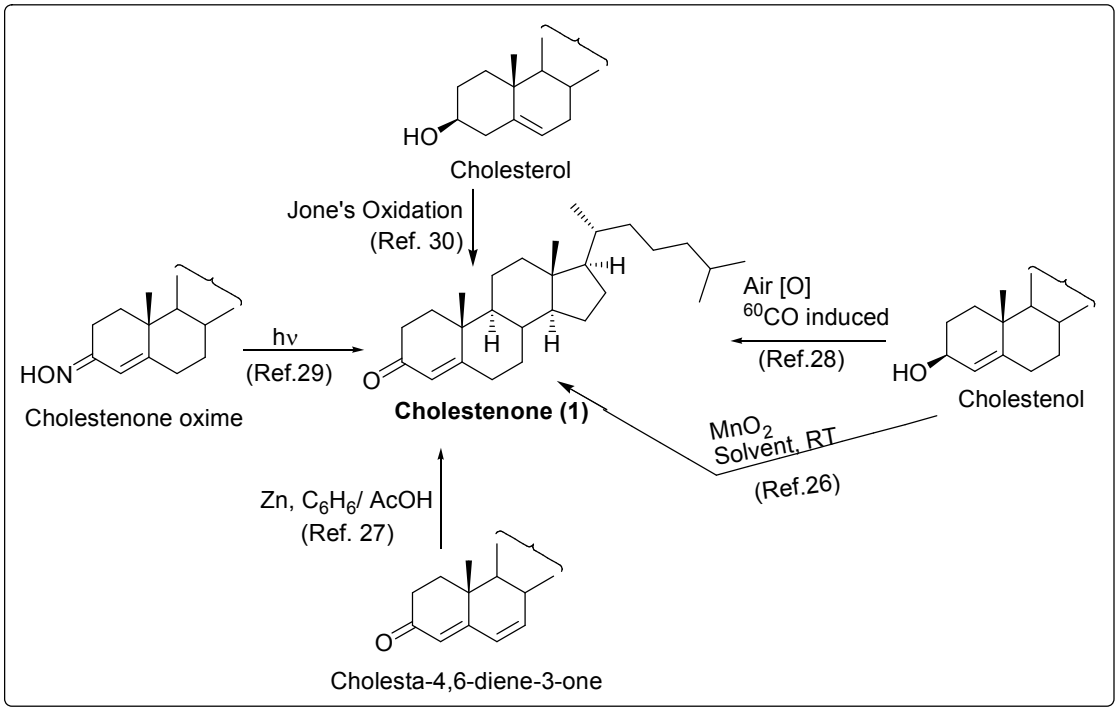
ES1. Natural sources of various ketosteroids.

Ketosteroid	Source(s)
 Cholestenone (**1**)	*Stelleta clarella*[1] *Patingera magellanica*[2] *Geodia cydonium*[3,4] *Cinachyra tarentina* [3,4] *Onchidiopsis variegate*[5] Rat serum[6] and in LDL and VLDL of normal human[7] Human gallstones and gallbladder bile[8]
 Stigmastenone (**2**)	*Patingera magellanica*[2] *Cryptomeria japonica D*[9] *Onchidiopsis variegate*[5]
 Cholest-4-en-3,6-dione (**3**)	*Onchidiopsis variegate*[5] *Geodia cydonium* [3,4] *Cinachyra tarentina* [3,4]
 Stigmast-4-en-3,6-dione (**16**)	*Sambucus ebulus*[10] *Echiumvulgare L.*[11]
	*Acantophora spicifera*[12]

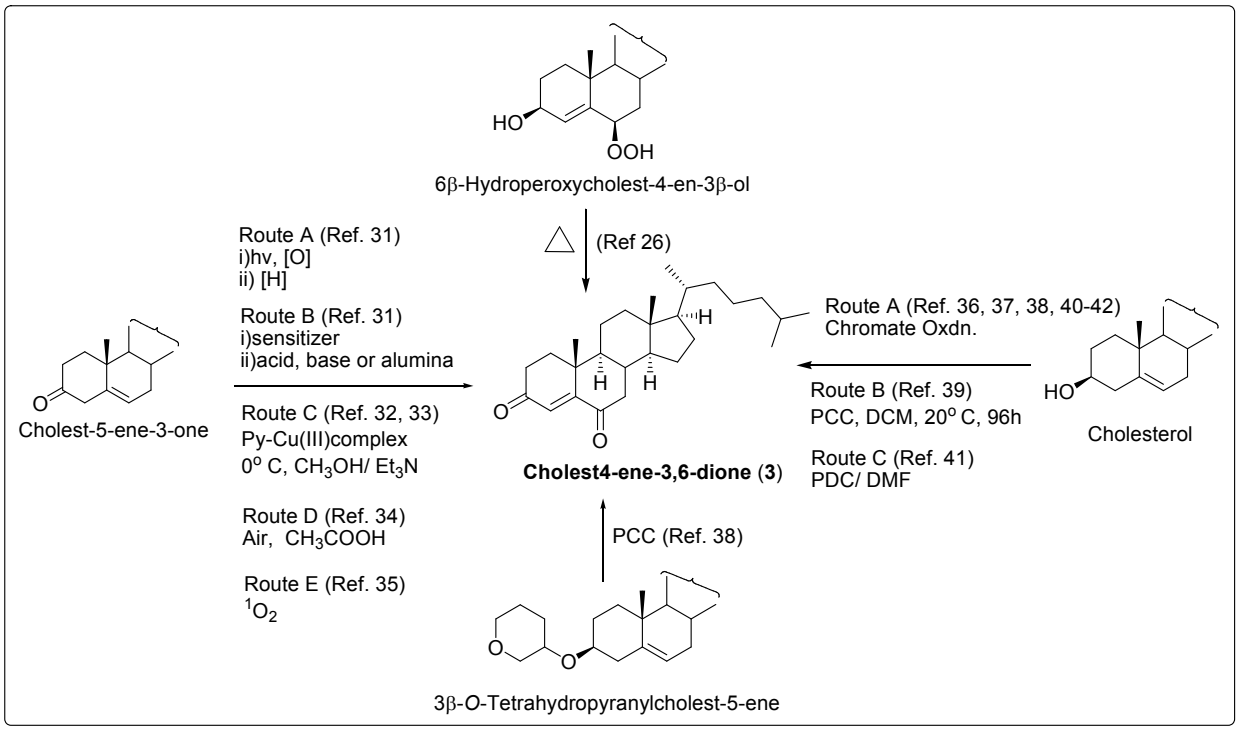
5α-Cholestane-3,6-dione (**5**)	
 5α-Stigmastane-3,6-dione (**6**)	*E. lagascae*[13]
 5α-Stigmastane -4,6-dione (**4**)	*Geodia cydonium* [3,4]
 Cholesta-3,5-dien-7-one (**9**)	*Fucus evanescens* [14] Rat liver[15] Livers of a group of cockerels.[16] In plasma of normal and diabetic human subjects.[17] In native LDL of the normocholesterolemic and hypercholesterolemic monkeys; in electronegatively charged LDL of hypercholesterolemic cynomologous monkeys.[18] In normal human liver as well as in alcoholic fatty liver, but the level was much higher in latter liver group. In human atherosclerotic lesions though this was found to be present but the level was very low as it was found to be a decomposition product of 7-keto cholesterol.[19] In extraordinary high level in rabbit's plasma.[20-21] Human gallstones and gallbladder bile[8]
 Stigmasta-3,5-dien-7-one (**10**)	*Gypsophila trichotoma.*[22]

 A-nor ketosteroid **12a and 12b**	*Acanthella cavernosa.*[23]
 Petrosterol-3,6-dione (**13**)	*Ianthella sp.* (Namyet Is., Vietnam)[24]
 ketosteroid **8**	*Cystoseira myrica*[25]
 cholesta-4,6-diene-3-one (**11**)	Human gallstones and gallbladder bile[8]

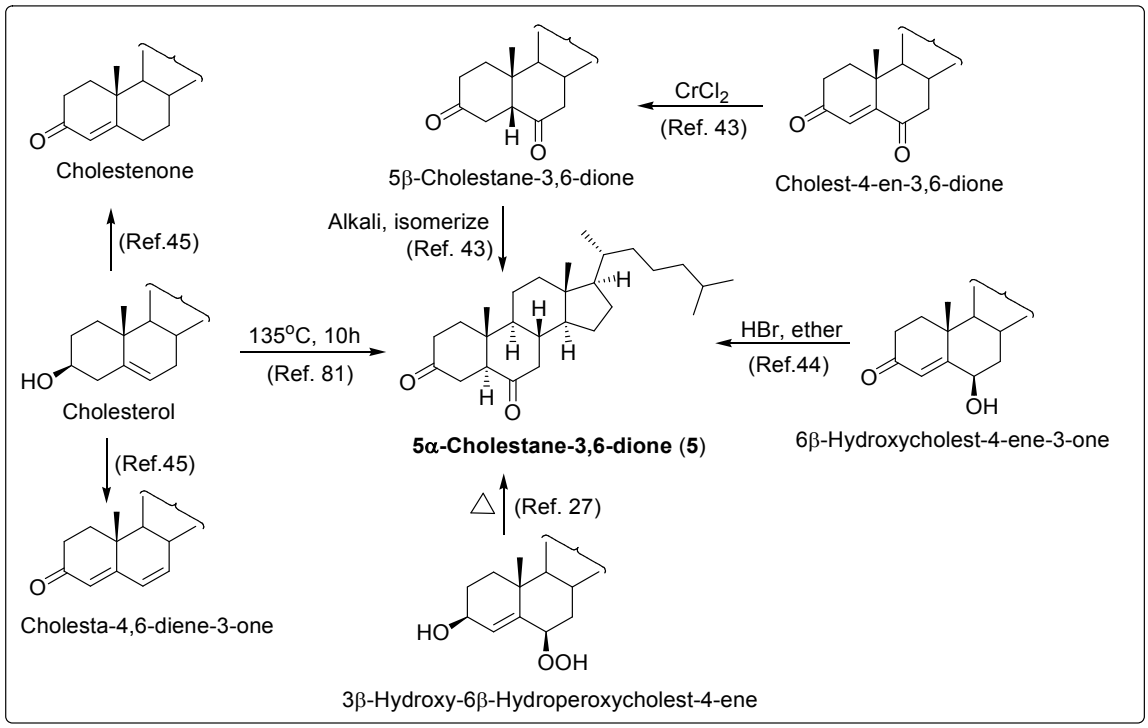
ES2. Schematic presentations for the earlier laboratory syntheses of various ketosteroids.



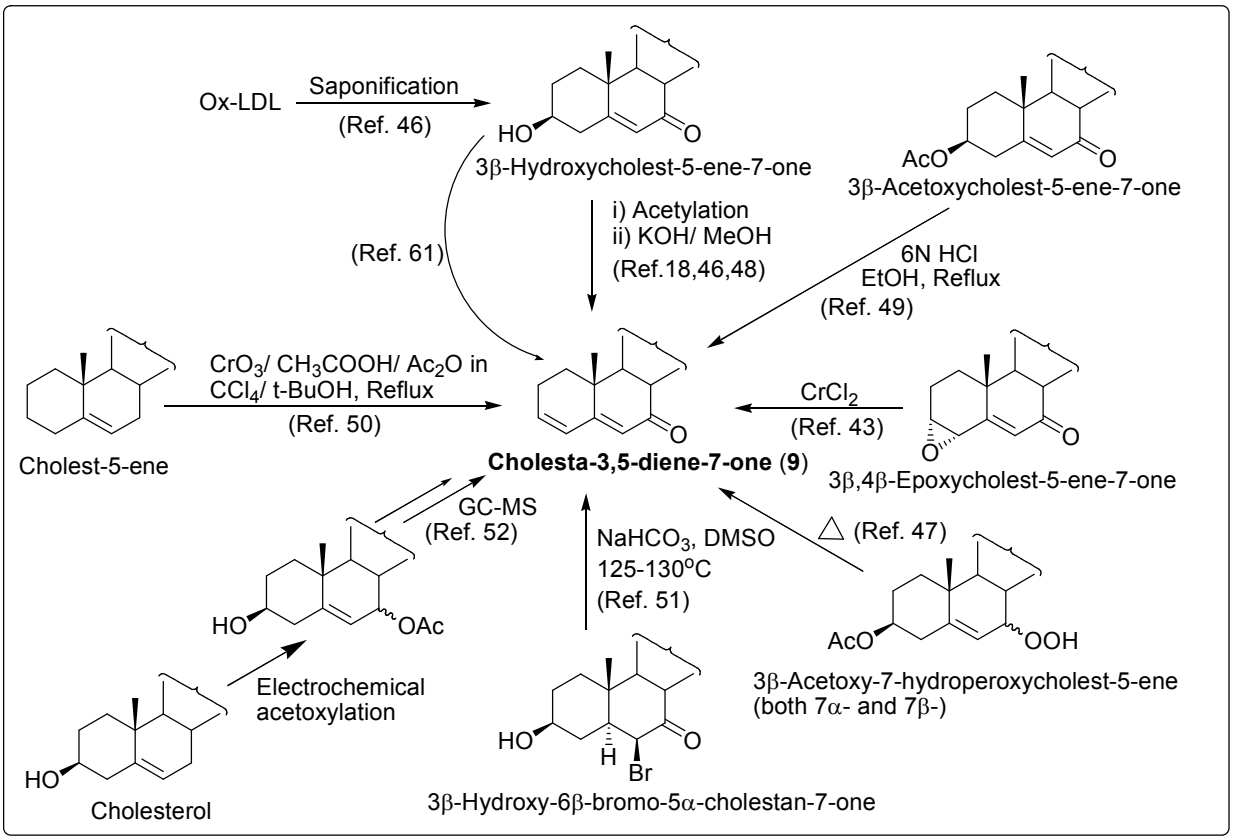
Scheme S1. Laboratory syntheses of cholestenone (**1**).



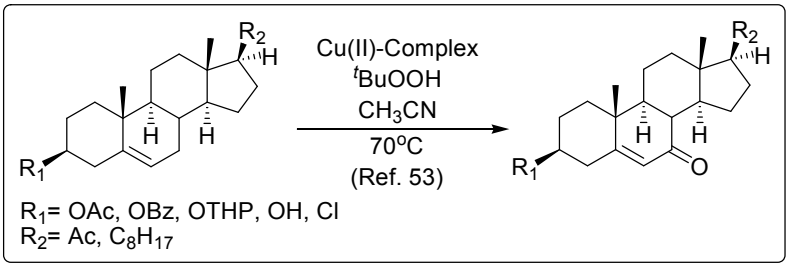
Scheme S2. Laboratory syntheses of cholest-4-ene-3,6-dione (**3**).



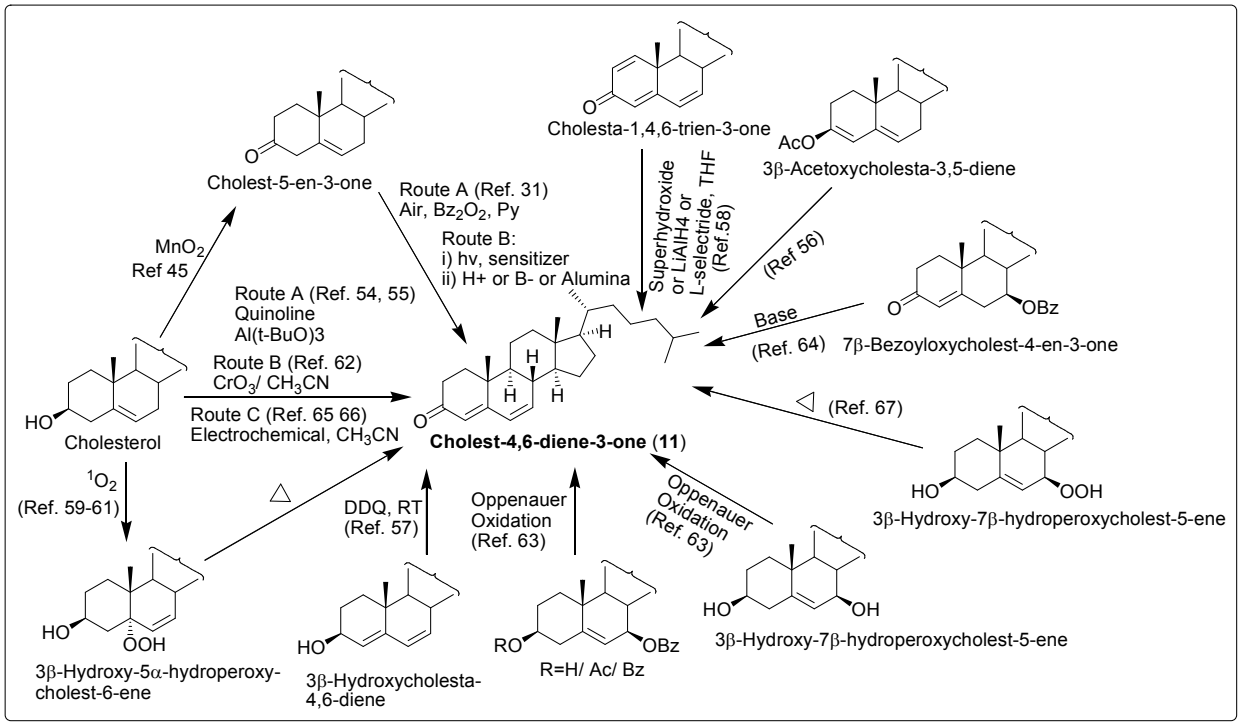
Scheme S3. Laboratory syntheses of 5α-cholestane-3,6-dione (**5**).



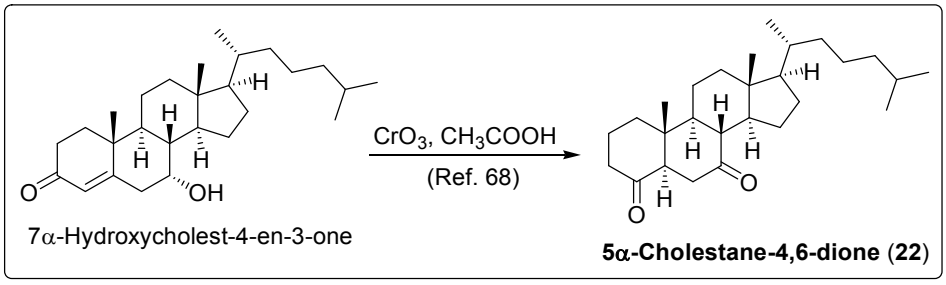
Scheme S4. Laboratory syntheses of cholesta-3,5-dien-7-one (**9**).



Scheme S5. Allylic oxidation of Δ^5-steroids to result the corresponding 5-ene-7-ones.

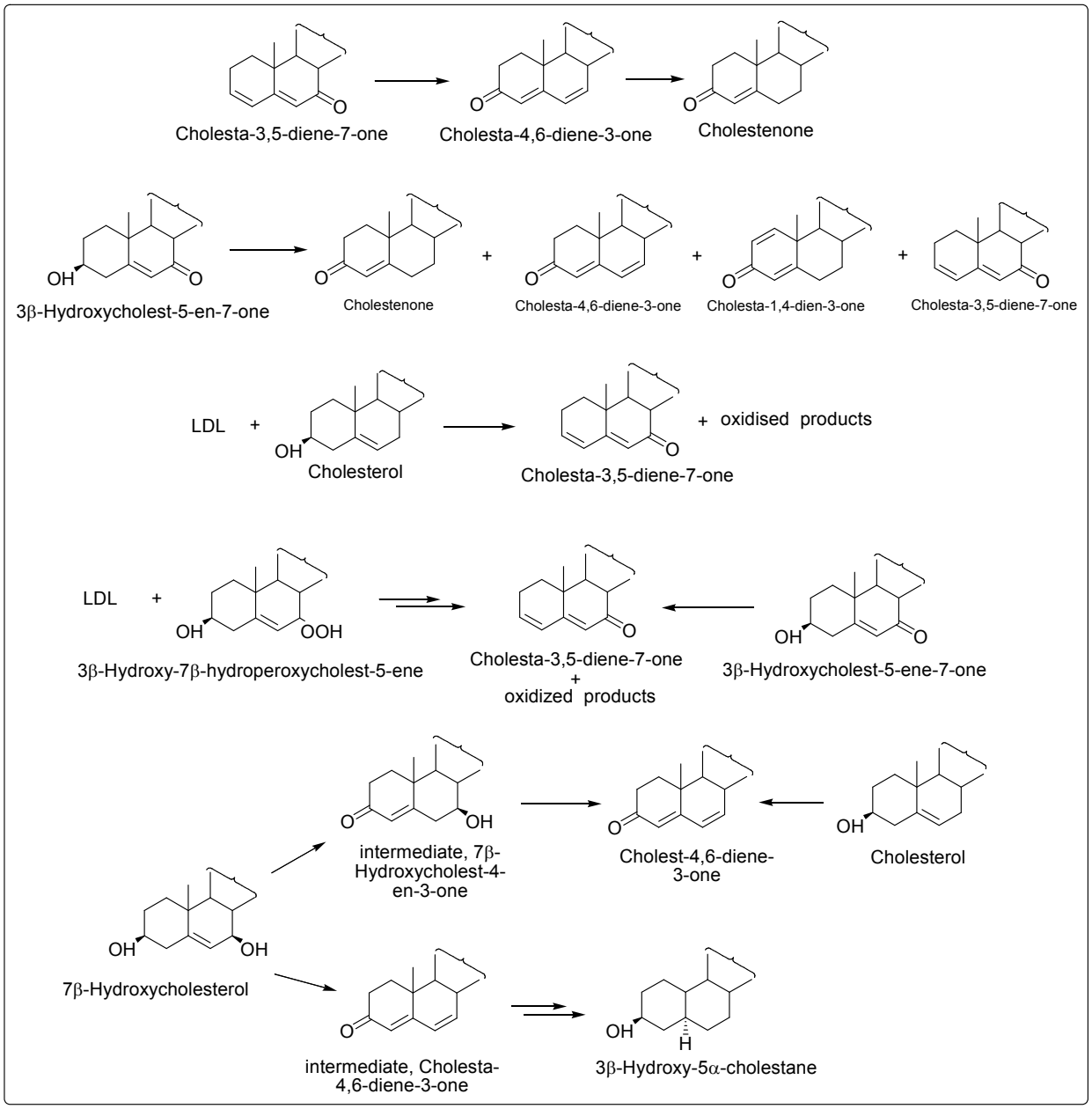


Scheme S6. Laboratory syntheses of cholesta-4,6-dien-3-one (**11**).



Scheme S7. Laboratory synthesis of 5α-cholestane-4,7-dione (**22**).

ES3. Schematic presentation for the bioconversion routes to some ketosteroids.



Scheme S8. Bioconversion of some ketosteroids.[18,69-78]

ES4. Biological reports of the ketosteroids related to the paper.[79]

Cholest-4-en-3-one was found to be weakly capable to inhibit sterol synthesis in cultured mouse cell.[80-81] It was capable of binding to antiestrogen-binding site (AEBS) of chicken liver cytosol[82] and to AEBS of the 10,000-*g* supernatant fraction of rat liver[83] and also to the AEBS of sonicated preparations of MCF7 cells (human breast cancer cell line).[84] When it was administered in the diet, it substantially decreased the body weight gain of rats, and increased markedly the adrenal gland weight.[85] It was also found to suppress the body weight gain of male and female mice,[86] and other ketosteroids such as cholesta-4,6-dien-3-one and cholest-4-ene-3,6-dione also showed similar activities. Cholest-4-ene-3,6-dione was found to have no antimicrobial activity against *S. cerevisiae (*ATCC 28383*)*, *S. aureus (53-154)*, *C. albicans (1180-79)* and *C. albicans(1663-86).*[39] But it showed significant inhibitory effects on sterol synthesis in intact animals.[87] 5α-Cholestane-3,6-dione has the potency to inhibit the sterol synthesis in mouse L-cells.[88] Stigmast-4-en-3,6-dione was found to inhibit the germination of barley by 40% at a concentration of 3mM and also showed moderate stimulatory effect at concentration below 0.1mM.[11] When the effect of 5α-Stigmastane-3,6-dione was tested on the reversal of multidrug resistance (MDR) in *human MDR1 gene-transfected mouse lymphoma cells*, it was found to be much more active.[89] Cholesta-3,5-dien-7-one was an "endogenous inhibitor of aldehyde dehydrogenase." It was a potent inhibitor of hepatic E1 isoenzyme (IC_{50} 5–10 μM) and also of mitocondrial E2 isoenzyme but at higher concentration only. Cholesta-4,6-dien-3-one and 7-ketocholesterol were inactive to E1 and E2 whereas E3 was unaffected by all the three compounds tested (Cholesta-3,5-dien-7-one, Cholesta-4,6-dien-3-one and 7-ketocholesterol).[90] According to Cao et al., cholesta-3,5-dien-7-one increased "steryl esters" and decreased the level of free desmosterol on the cellular levels.[91] Highly concentrated cholesta-3,5-dien-7-one showed slightly stimulatory effects when leveled oleic acid was incorporated into the triglycerides of human fibroblasts.[92] Selley et al. reported that this oxosterol "potentiated the aggregation of human platelets induced by ADP, thrombin, or collagen." [93] Dietary administration of this compound to cockerels showed no effect on serum cholesterol level, no or little effect on liver weight and increased effect on intestines weight.[94] Cholest-4-en-3-one, cholesta-4,6-dien-3-one and cholesta-3,5-dien-7-one are found to be present in human gallstones, and gallbladder bile can cause apoptosis in cultured gallbladder epithelial cells when the compounds were uptaken from bile and then were incorporated into the mitochondria. As a result cytochrome-C was released into the cytosol.[95] It has been observered that in certain cases introduction of a keto group at 7-position increased its bioactivity as Δ^5-7-keto steroids are able to cell replication and hence more toxic to cancerous cells, e.g., 5-androstene-7,17-dione.[96]

ES5. Copies of ^{1}H and ^{13}C NMR spectra of the isolated products.

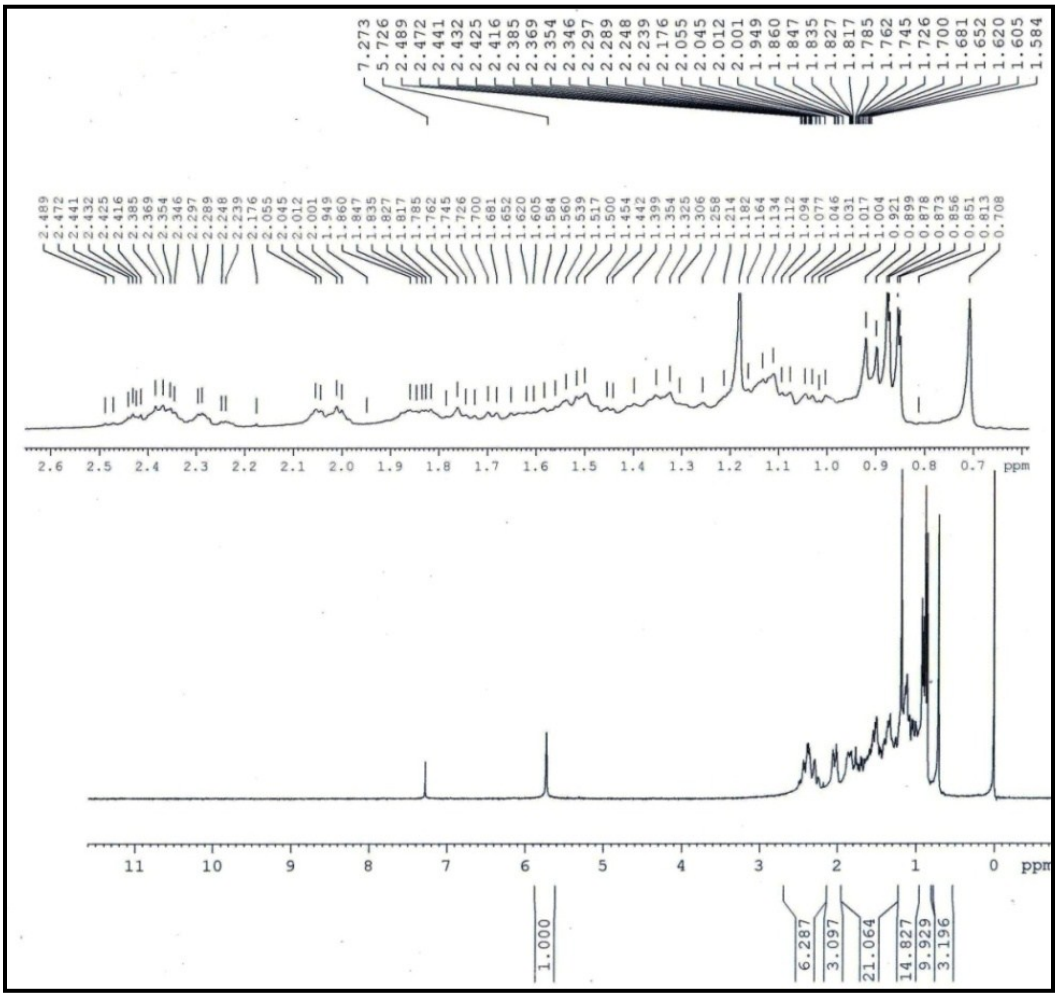


Figure S9. ^{1}H NMR spectrum of cholestenone (**1**).

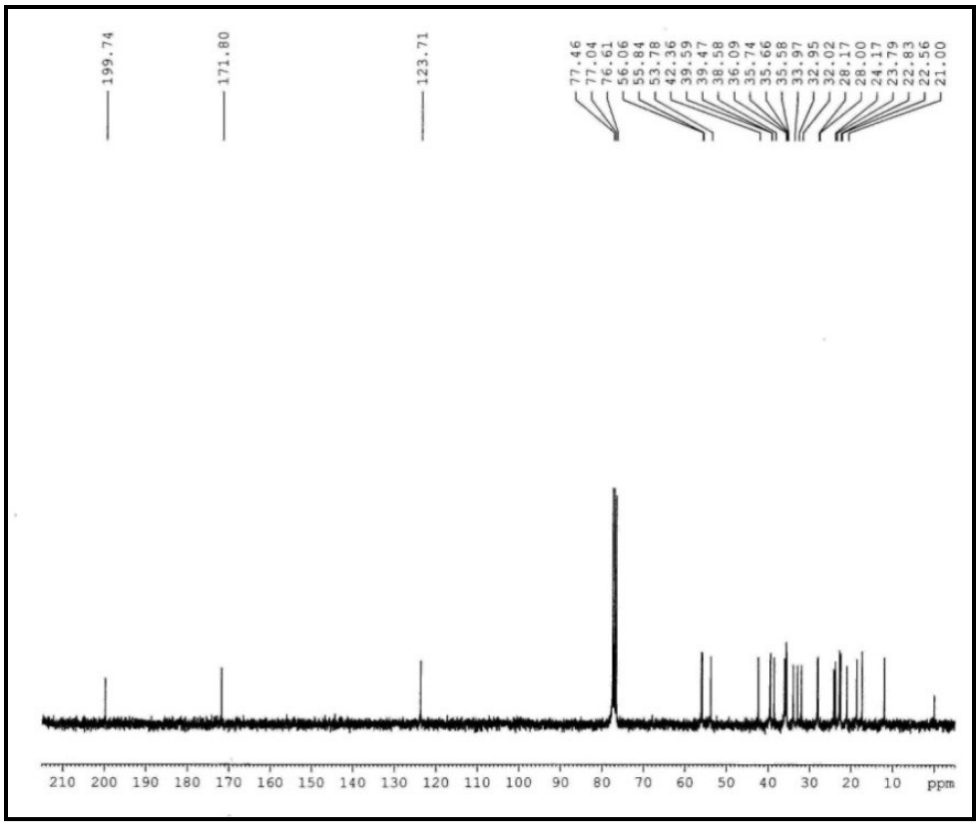


Figure S10. ^{13}C NMR spectrum of cholestenone (**1**).

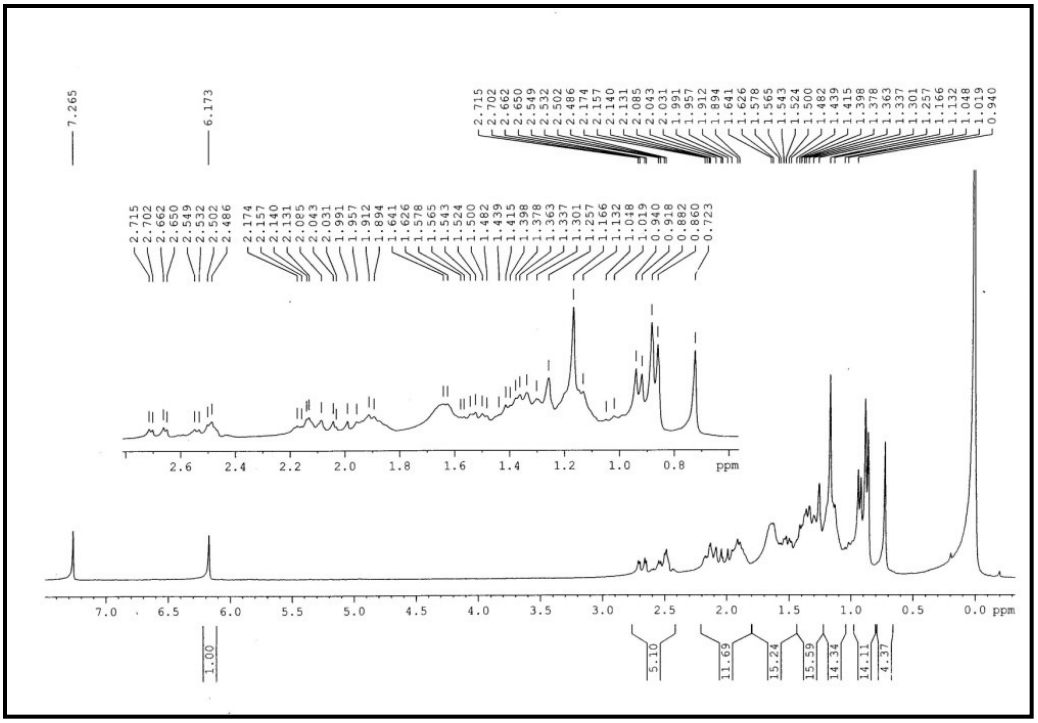


Figure S11. ^{1}H NMR spectrum of cholest-4-ene-3,6-dione (**3**).

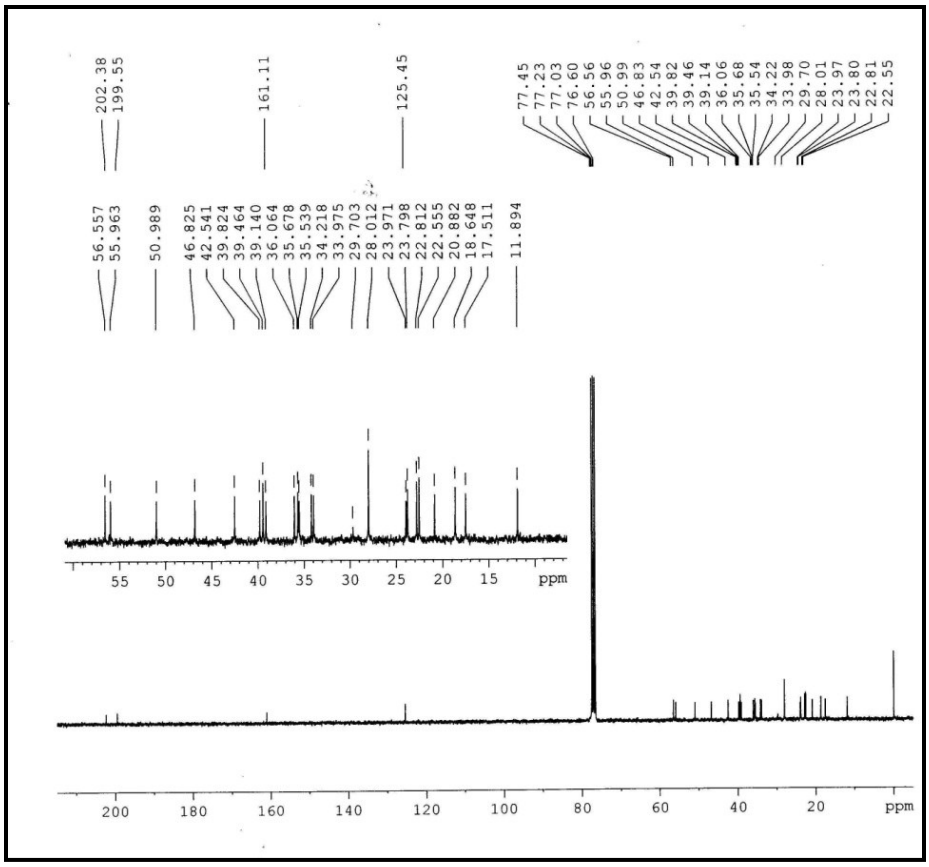


Figure S12. ^{13}C NMR spectrum of cholest-4-ene-3,6-dione (**3**).

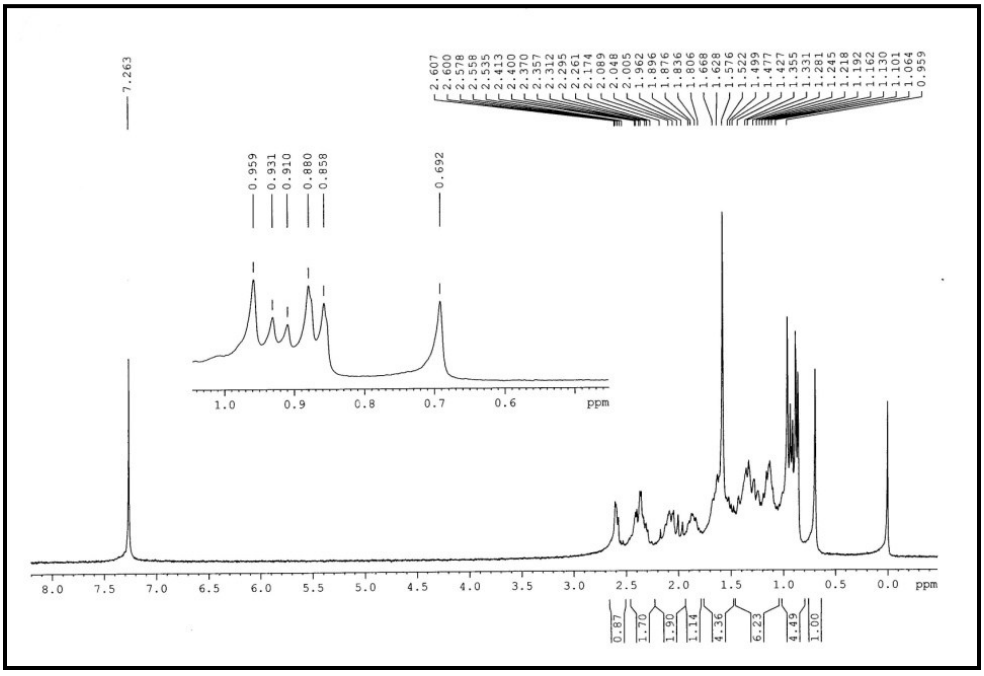


Figure S13. ^{1}H NMR spectrum of 5α-cholestan-3,6-dione (**5**).

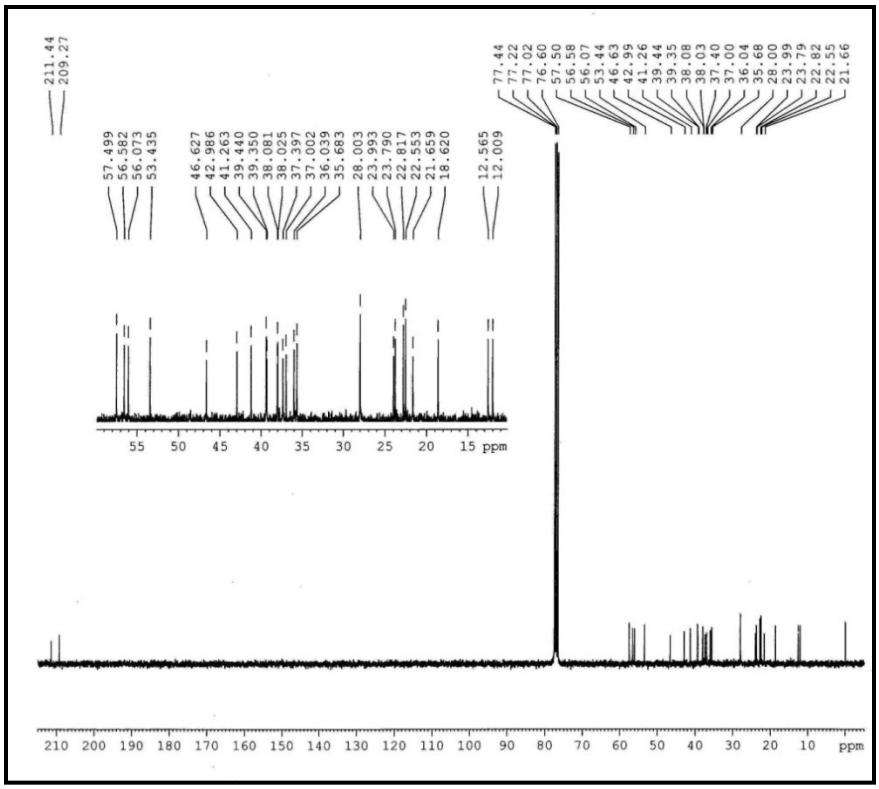


Figure S14. ^{13}C NMR spectrum of 5α-cholestan-3,6-dione (**5**).

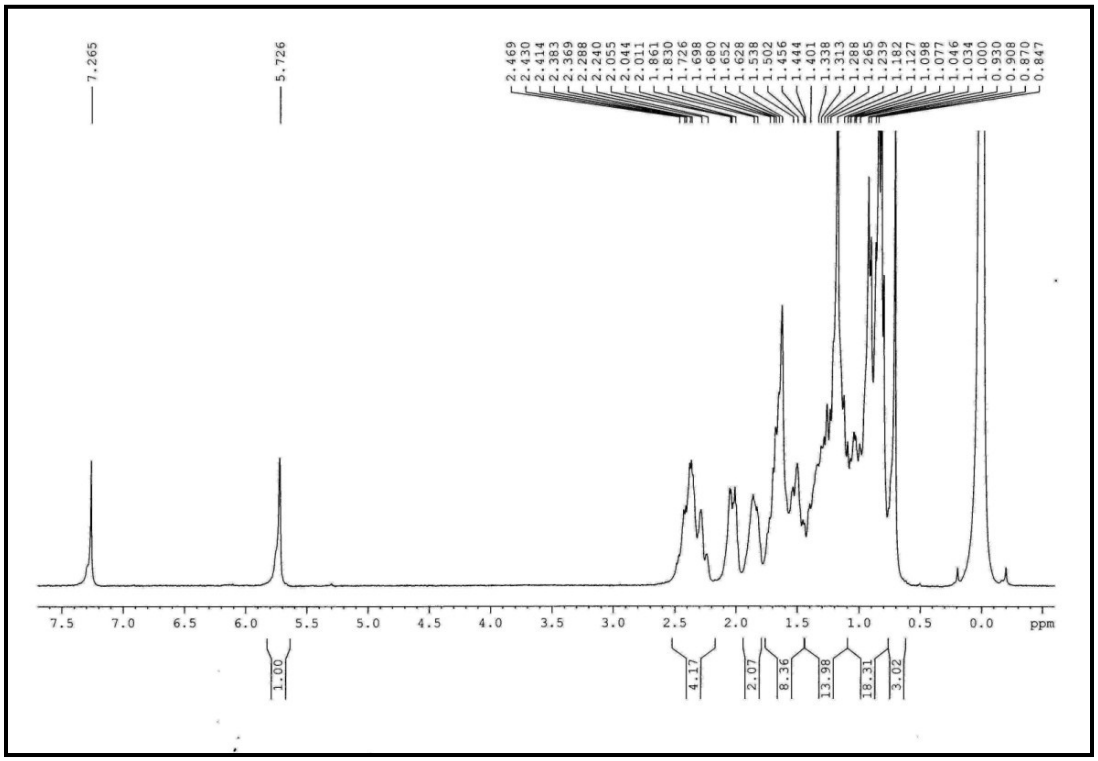


Figure S15. ^{1}H NMR spectrum of stigmastenone (**2**).

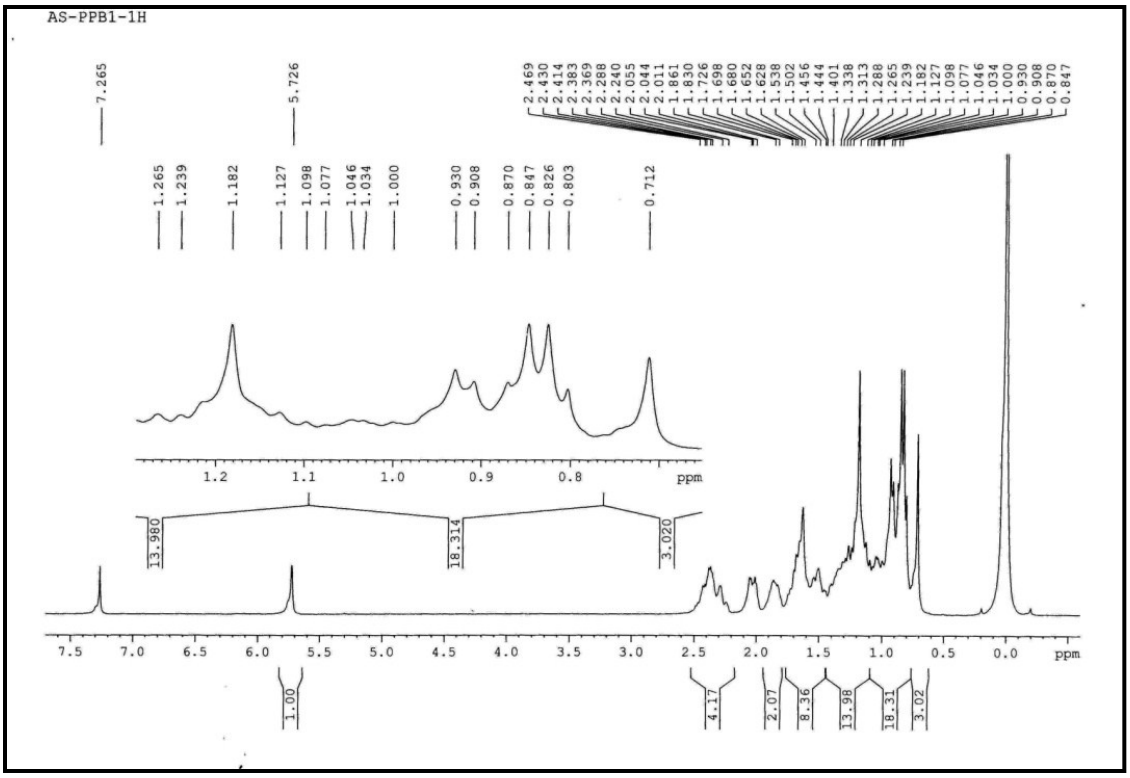


Figure S16. Extended ^{1}H NMR spectrum of stigmastenone (**2**).

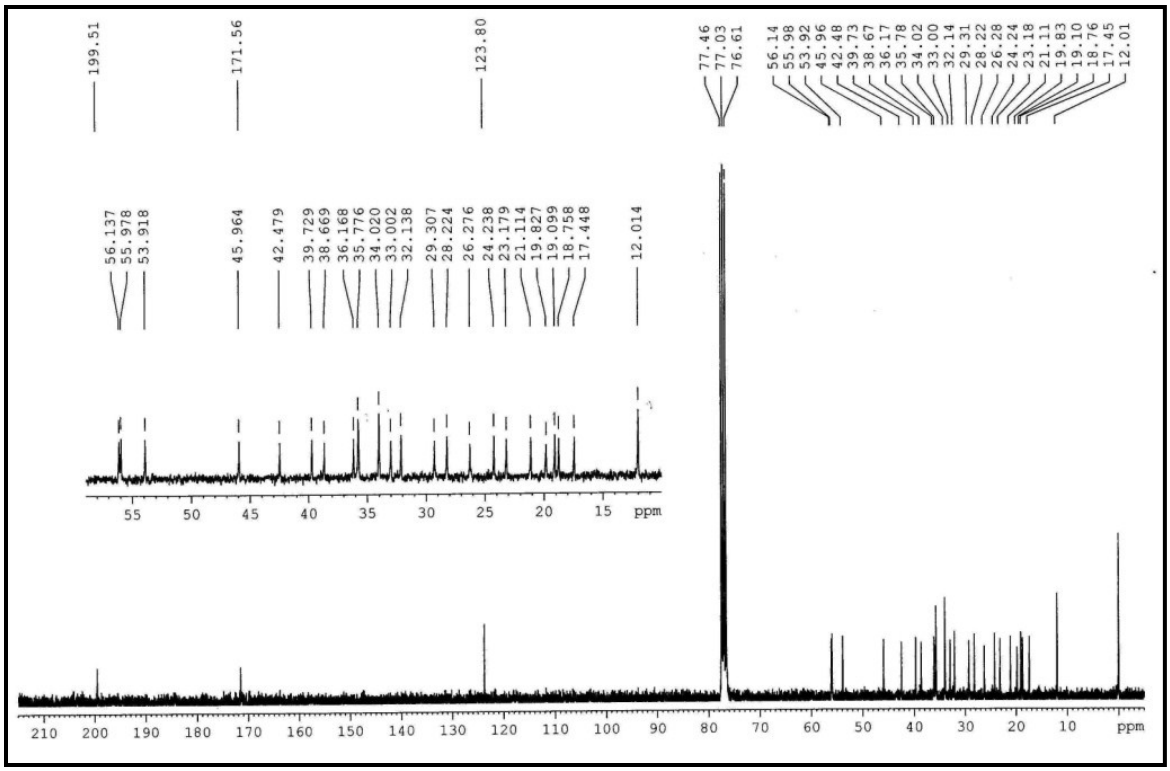


Figure S17. ^{13}C NMR spectrum of stigmastenone (**2**).

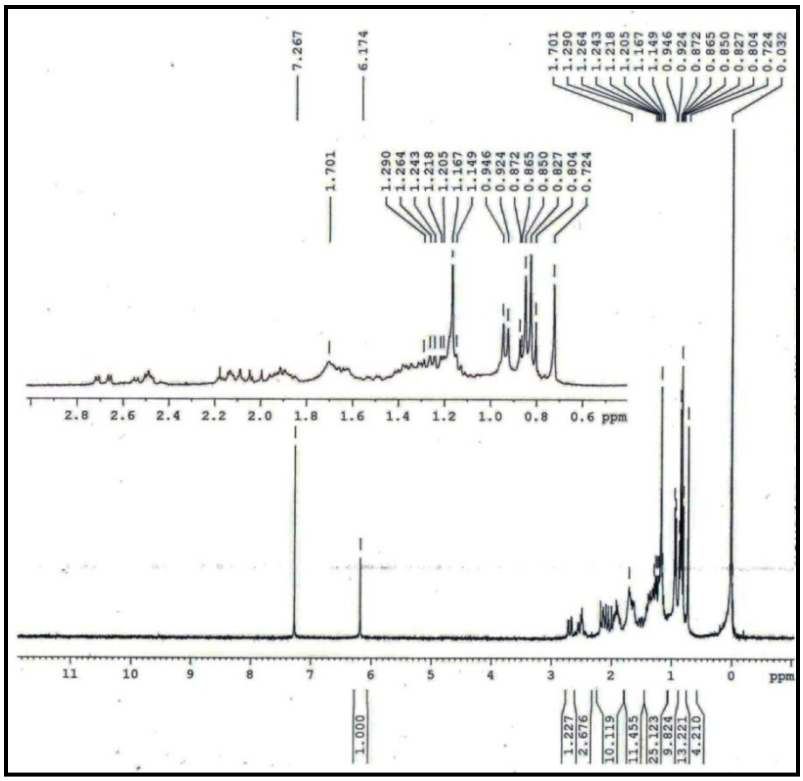


Figure S18. ^{1}H NMR spectrum of stigmast-4-ene-3,6-dione (**16**).

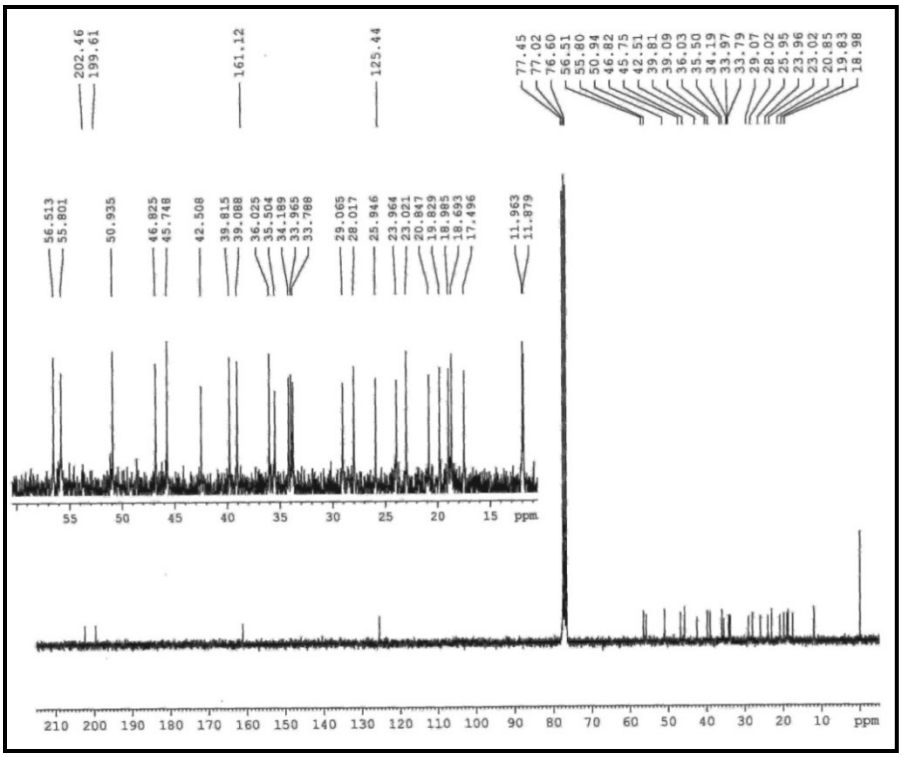


Figure S19. ^{13}C NMR spectrum of stigmast-4-ene-3,6-dione (**16**).

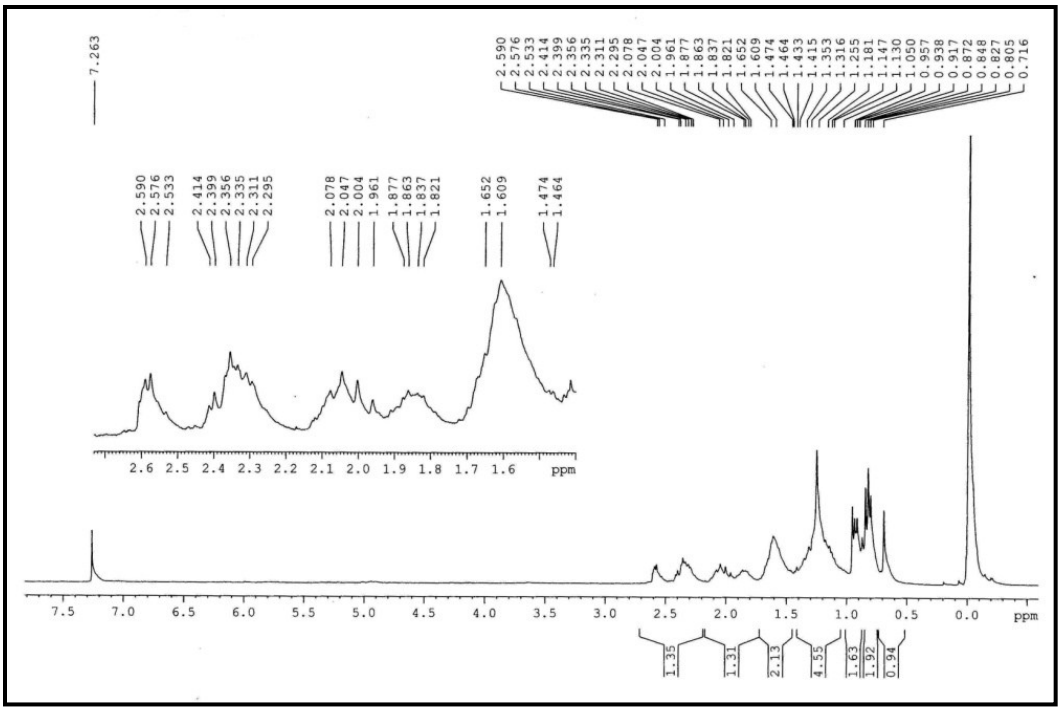


Figure S20. ^{1}H NMR spectrum of 5α-stigmastane-3,6-dione (**6**).

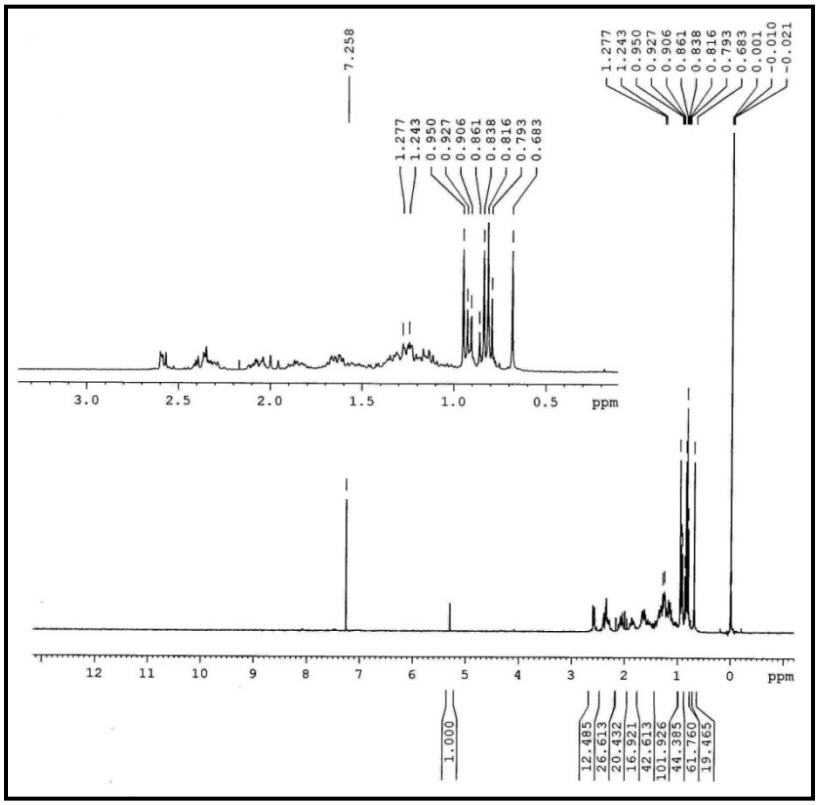


Figure S21. ^{1}H NMR spectrum (expanded) of 5α-stigmastane-3,6-dione (**6**).

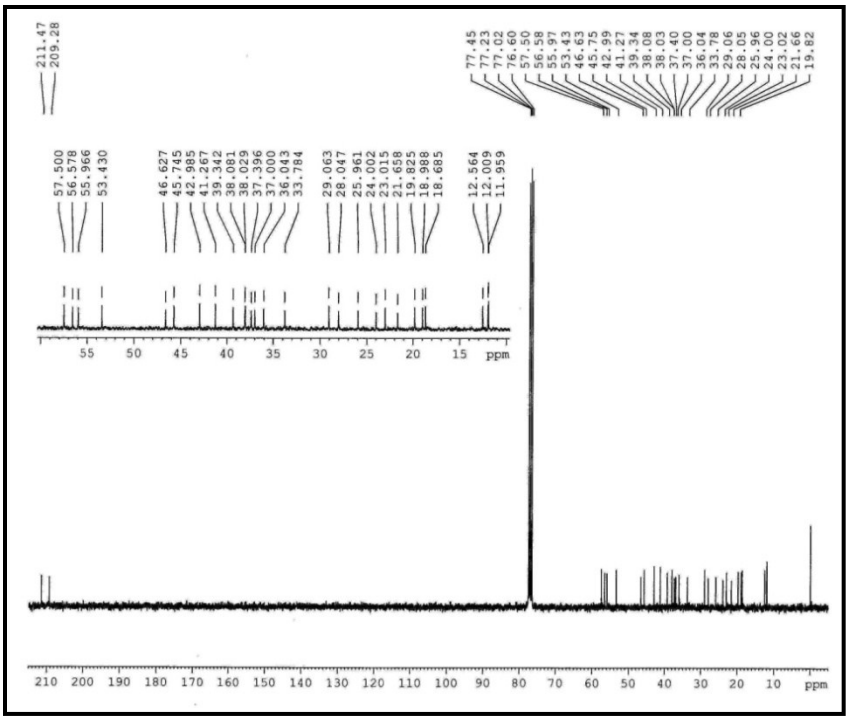


Figure S22. ^{13}C NMR spectrum of 5α-stigmastane-3,6-dione (**6**).

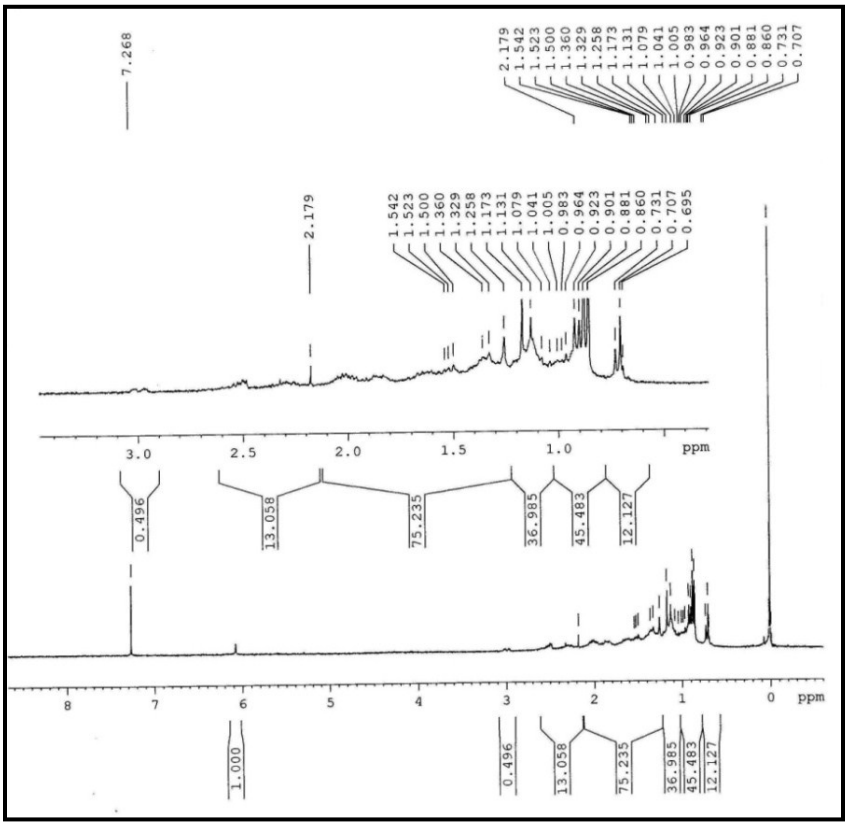


Figure S23. ^{1}H NMR spectrum of cholest-5-en-7-one (**19**).

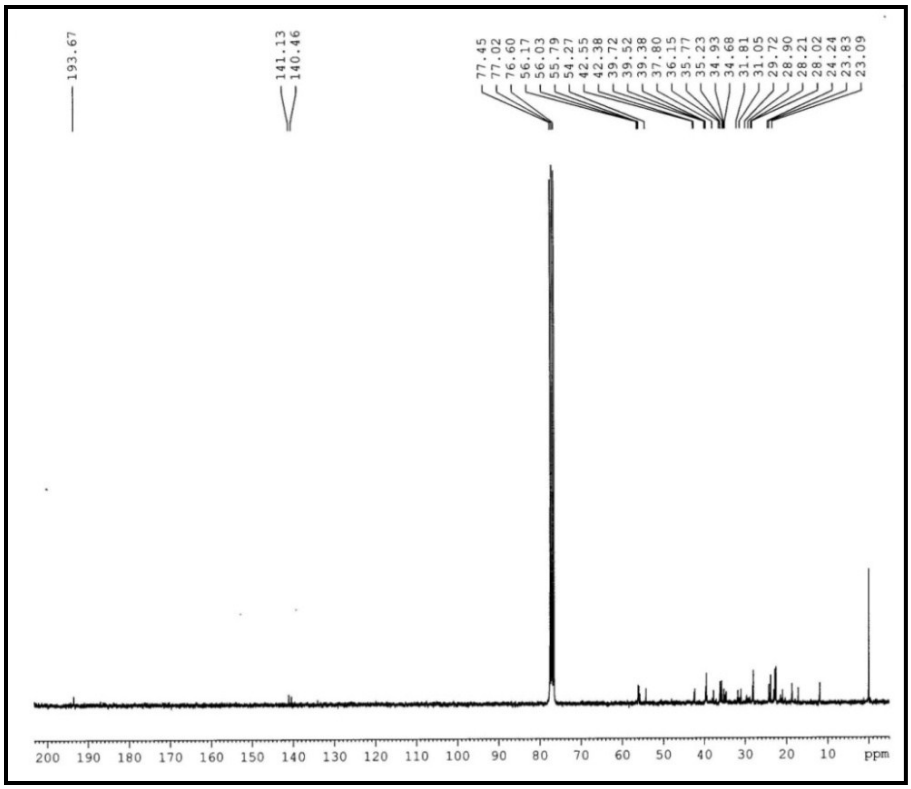


Figure S24. ^{13}C NMR spectrum of cholest-5-en-7-one (**19**).

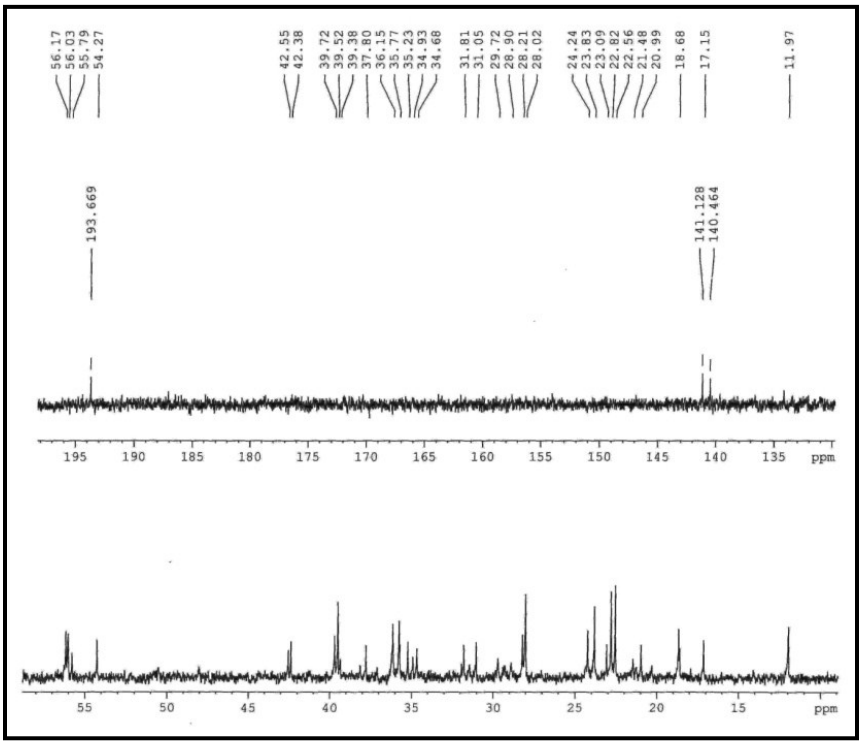


Figure S25. Expanded ^{13}C NMR spectrum of cholest-5-en-7-one (**19**).

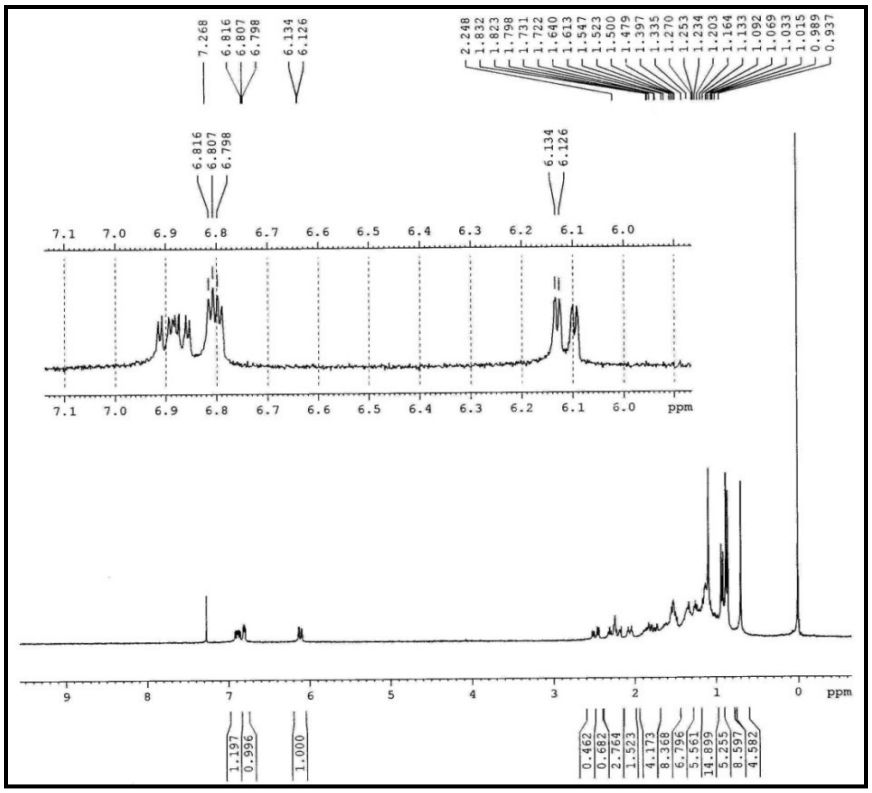


Figure S26. [1]H NMR spectrum of cholesta-3,5-diene-7-one (**9**).

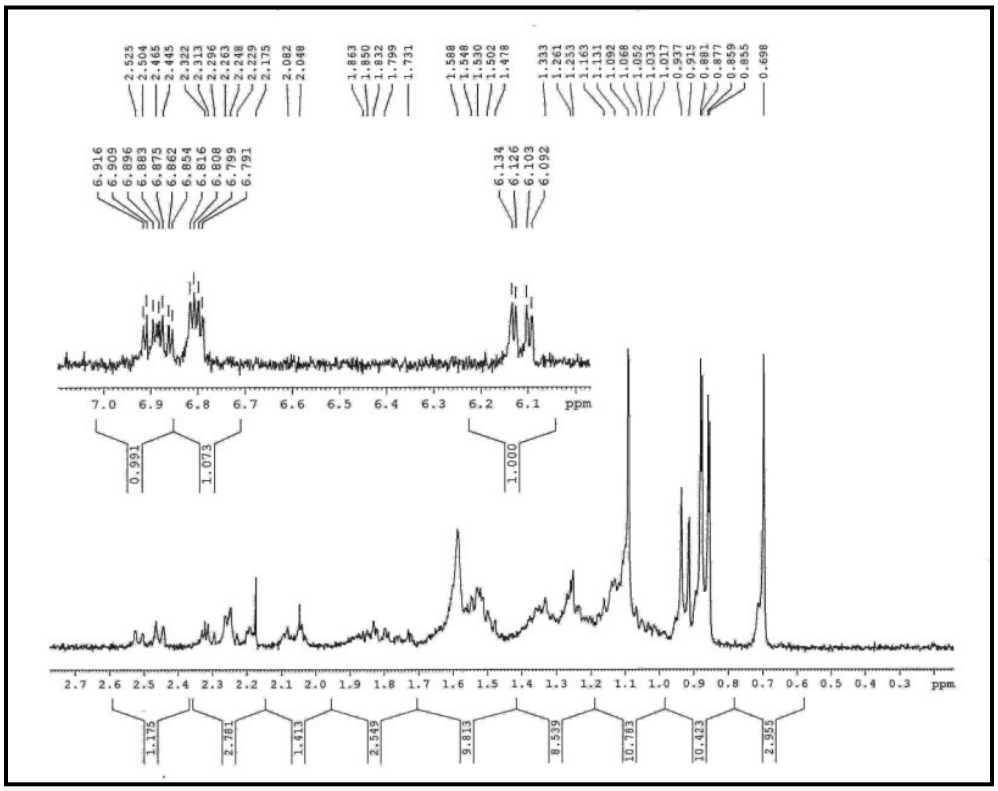


Figure S27. [1]H NMR spectrum (partially expanded) of cholesta-3,5-diene-7-one (**9**).

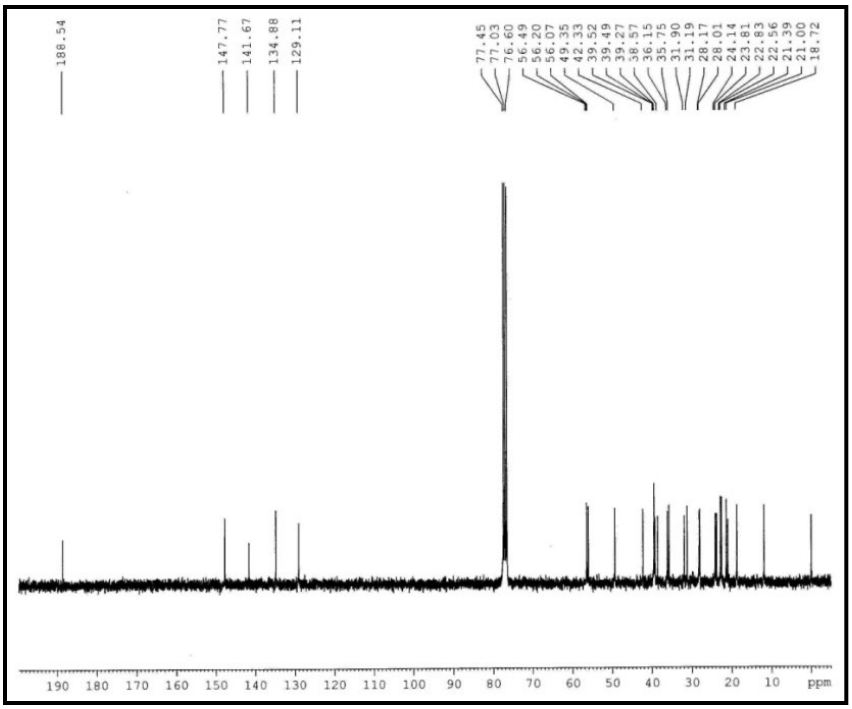


Figure S28. ^{13}C NMR spectrum of cholesta-3,5-dien-7-one (**9**).

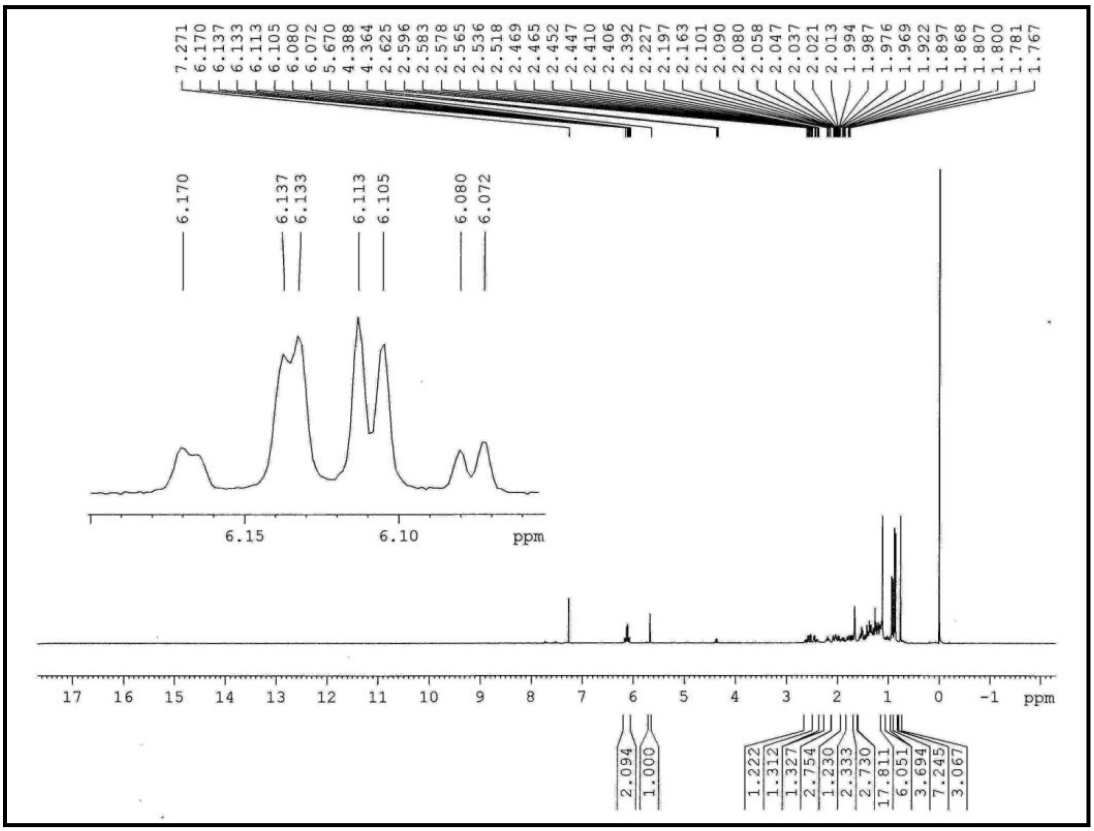


Figure S29. ^{1}H NMR spectrum of cholesta-4,6-diene-3-one (**11**).

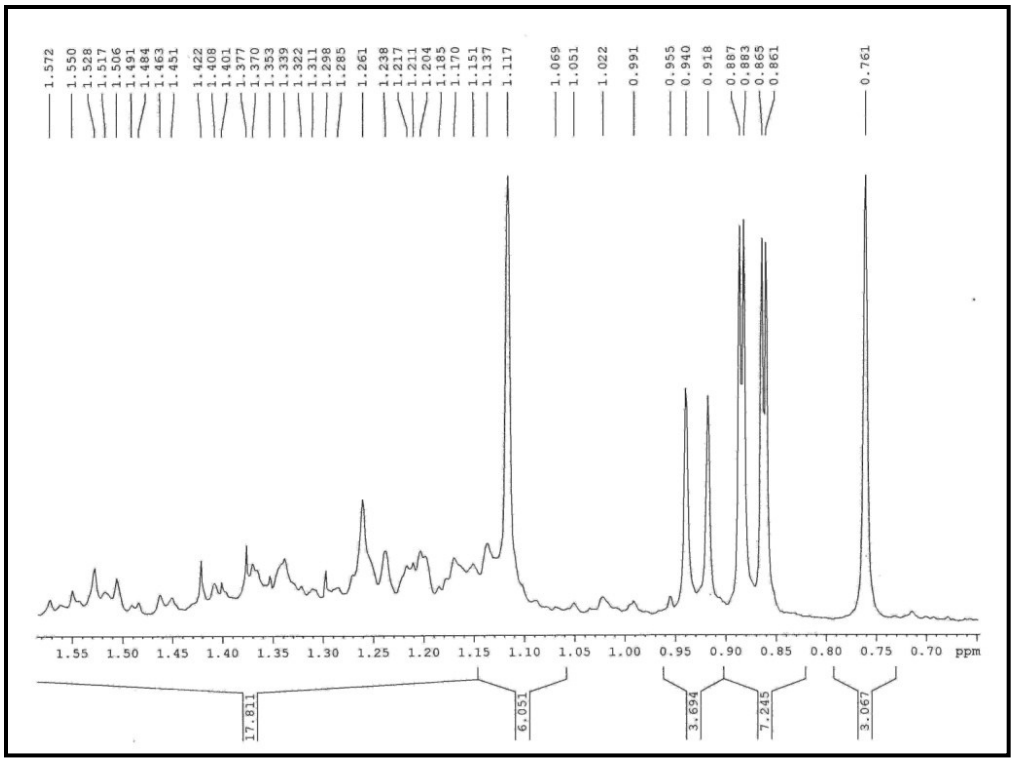


Figure S30. ^{1}H NMR spectrum (expanded methyls) of cholesta-4,6-diene-3-one (**11**).

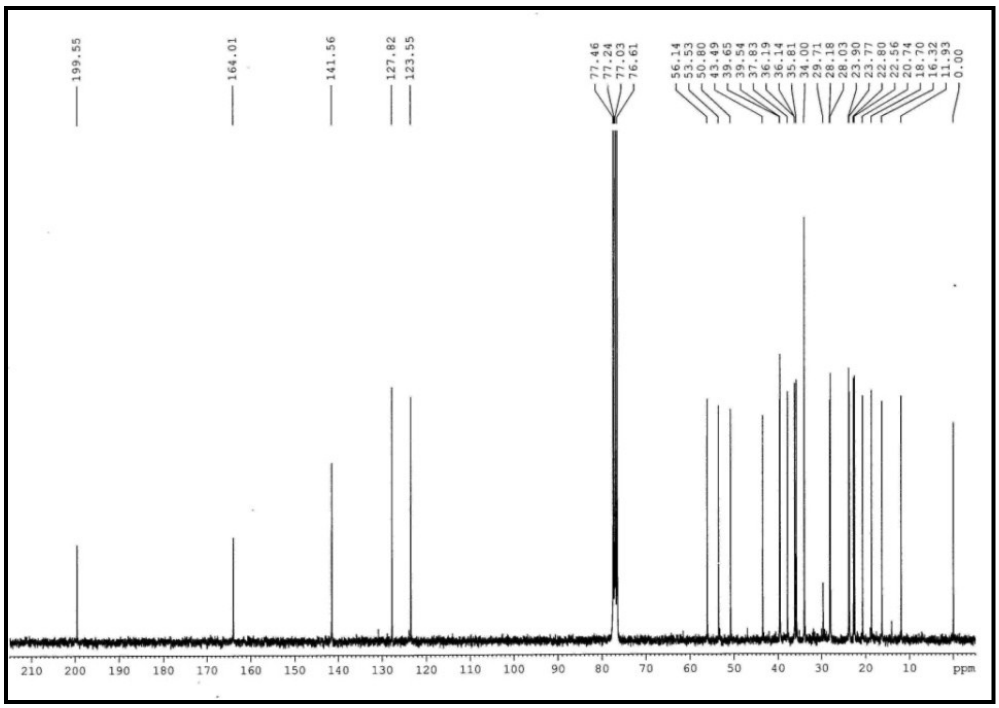


Figure S31. ^{13}C NMR spectrum of cholesta-4,6-diene-3-one (**11**).

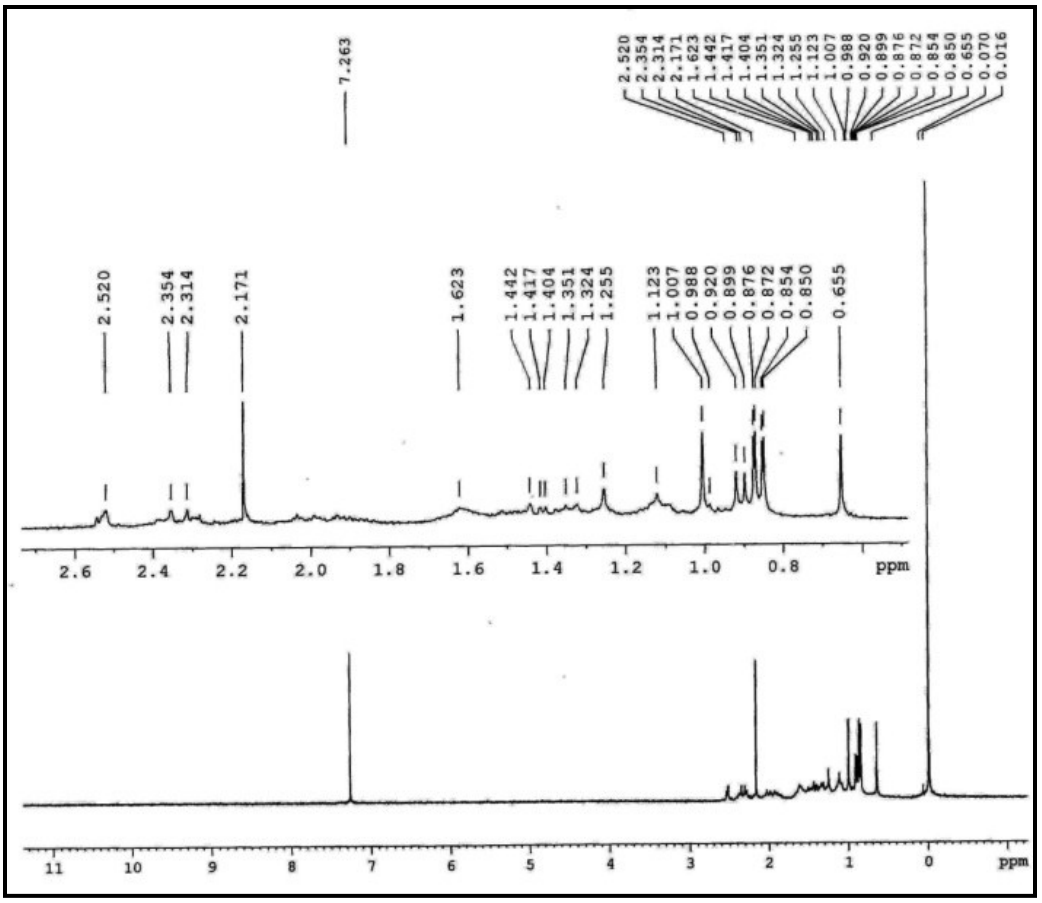


Figure S32. ^{1}H NMR spectrum of cholest-4,7-dione (**22**).

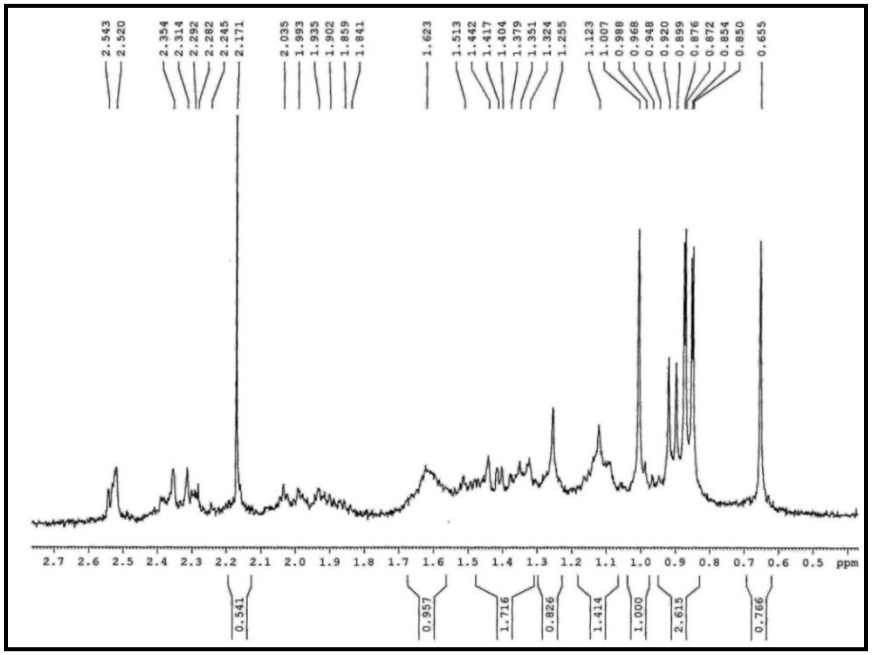


Figure S33. Extended ^{1}H NMR spectrum of cholest-4,7-dione (**22**).

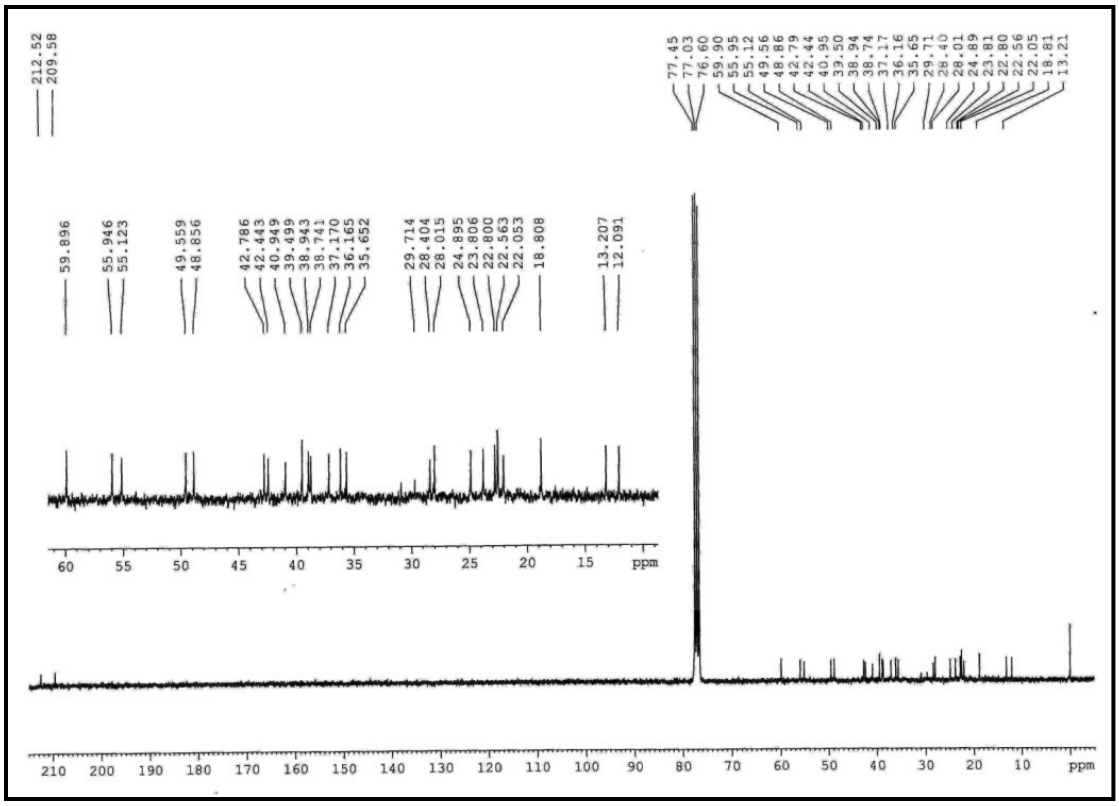


Figure S34. ^{13}C NMR spectrum of cholest-4,7-dione (**22**).

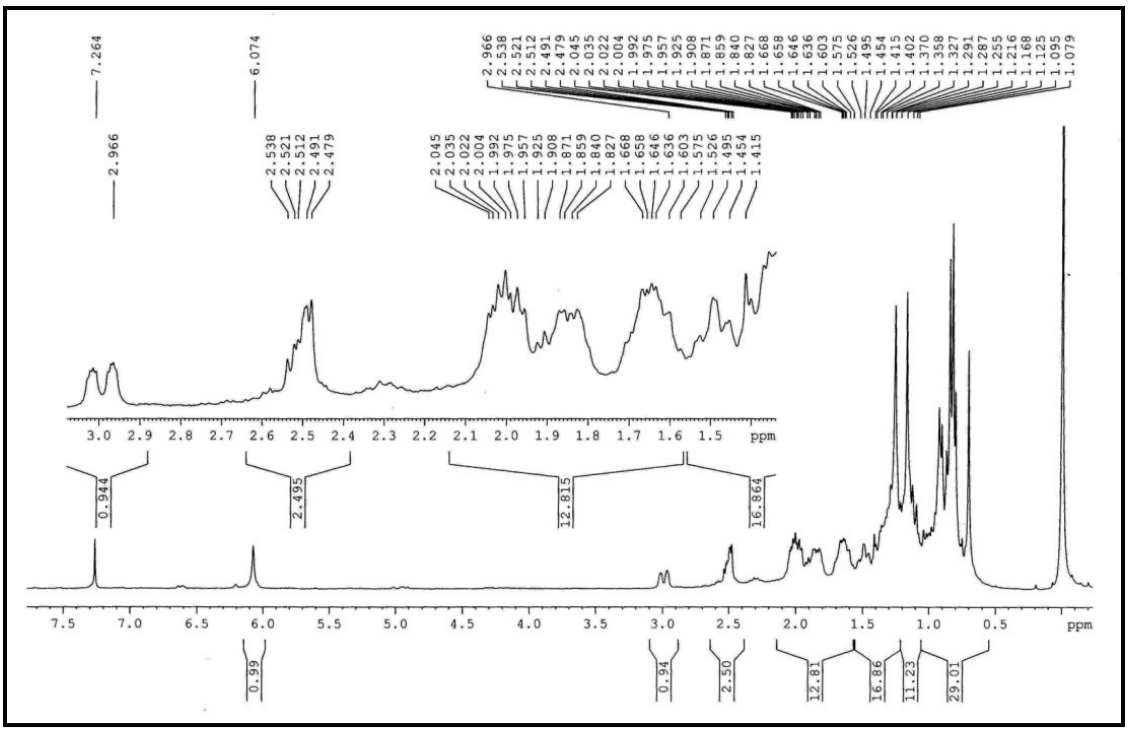


Figure S35. ^{1}H NMR spectrum of stigmast-5-en-7-one (**20**).

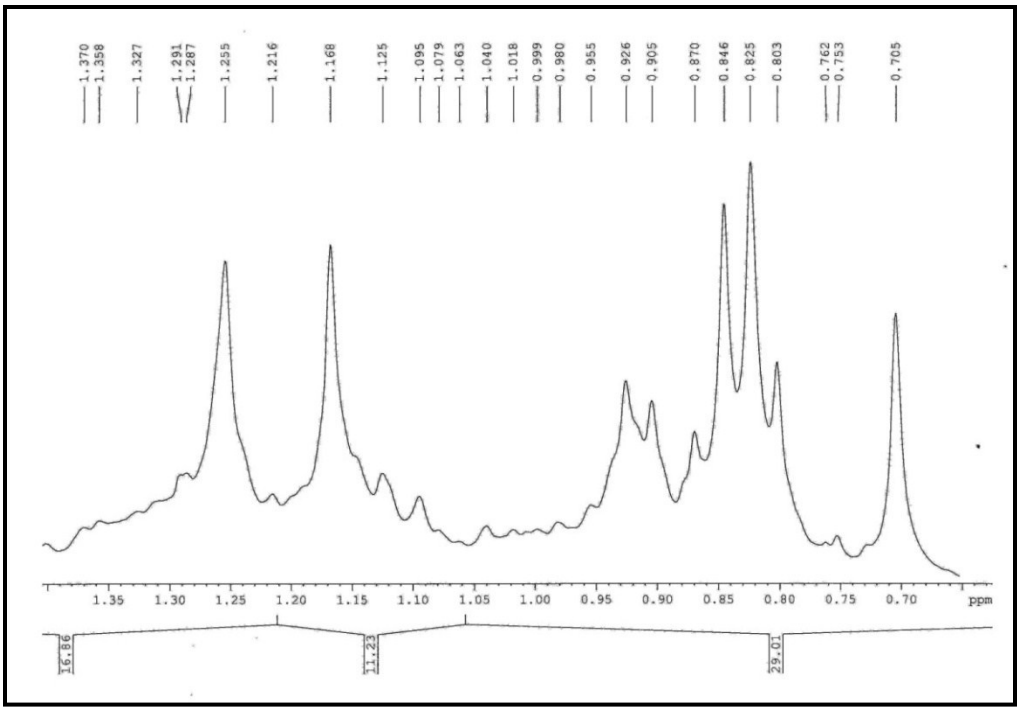


Figure S36. Partially expanded ^{1}H NMR spectrum of stigmast-5-en-7-one (**20**).

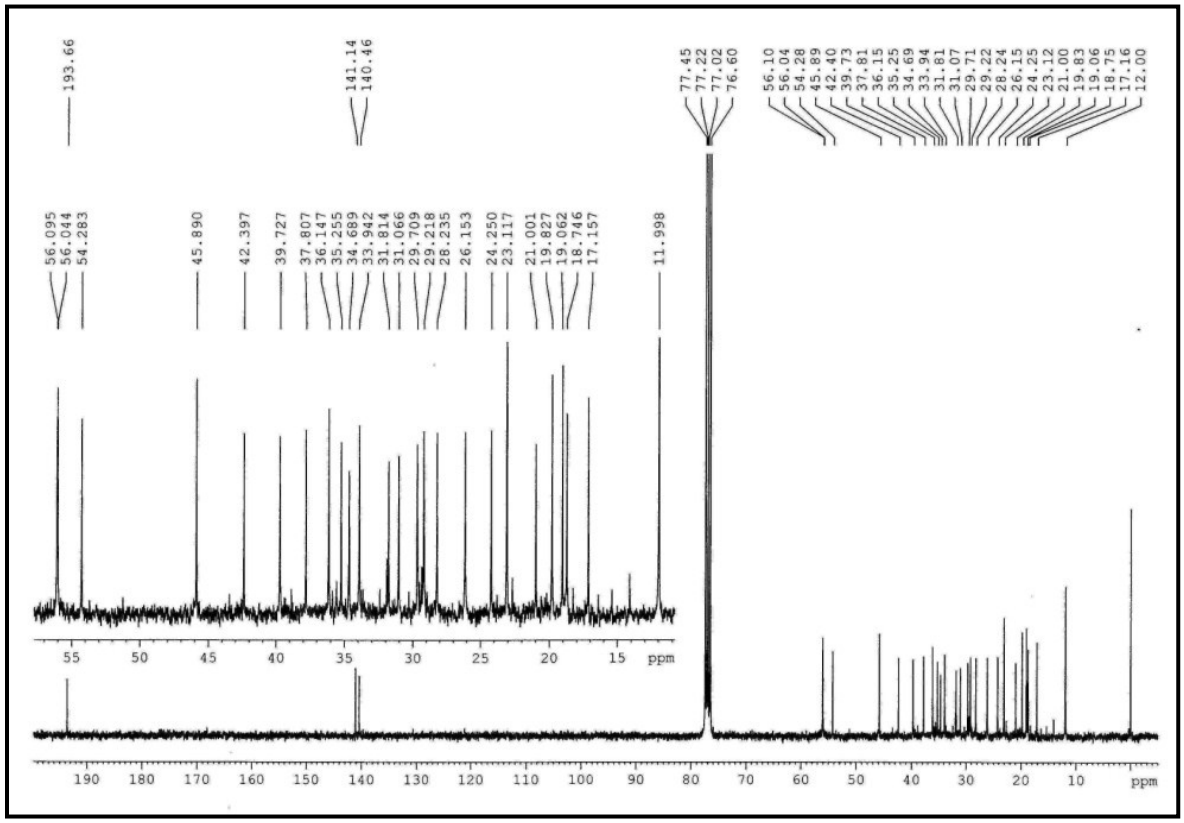


Figure S37. ^{13}C NMR spectrum of stigmast-5-en-7-one (**20**).

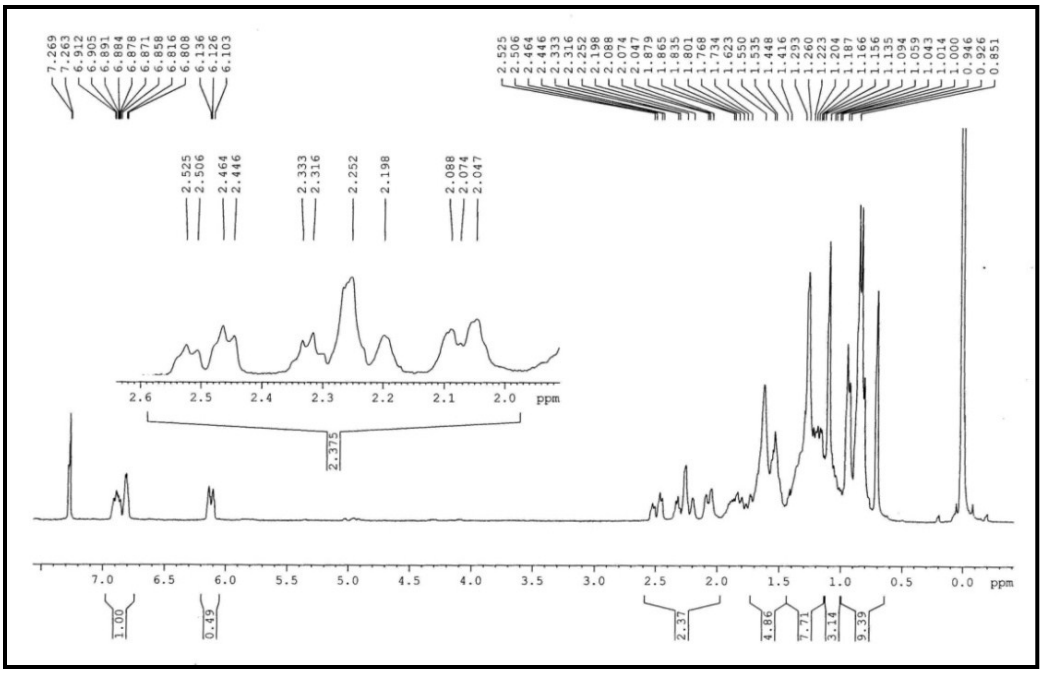


Figure S38. [1]H NMR spectrum of stigmasta-3,5-diene-7-one (**10**).

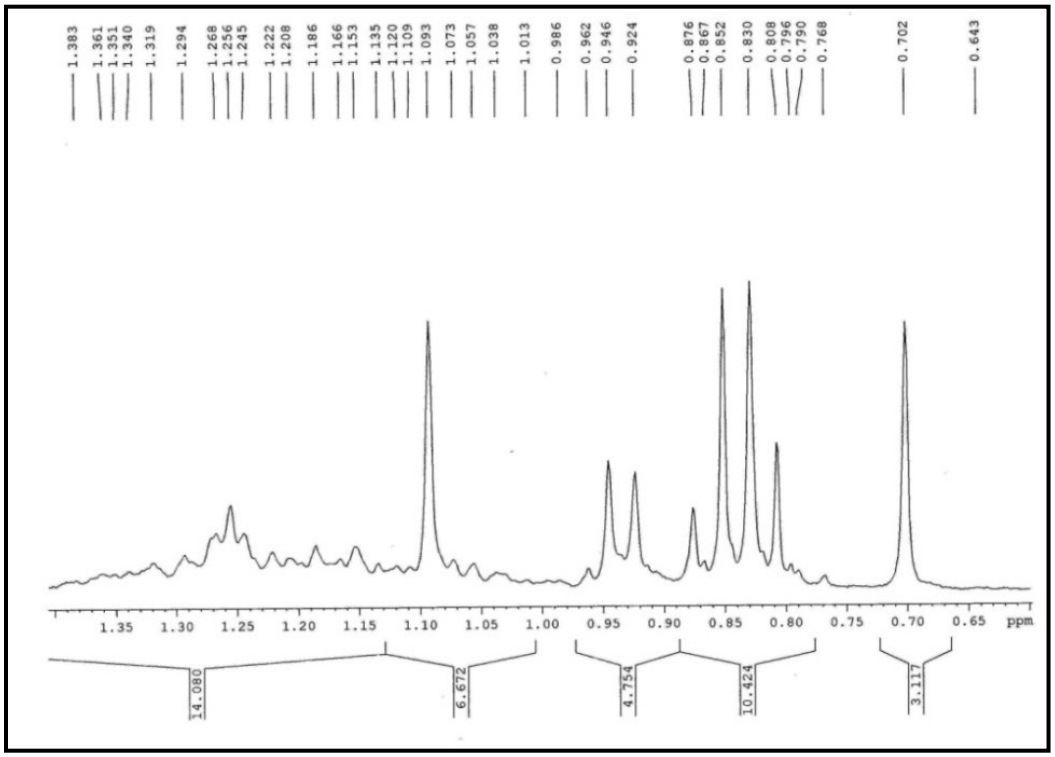


Figure S39. [1]H NMR spectrum (expanded methyls) of stigmasta-3,5-diene-7-one (**10**).

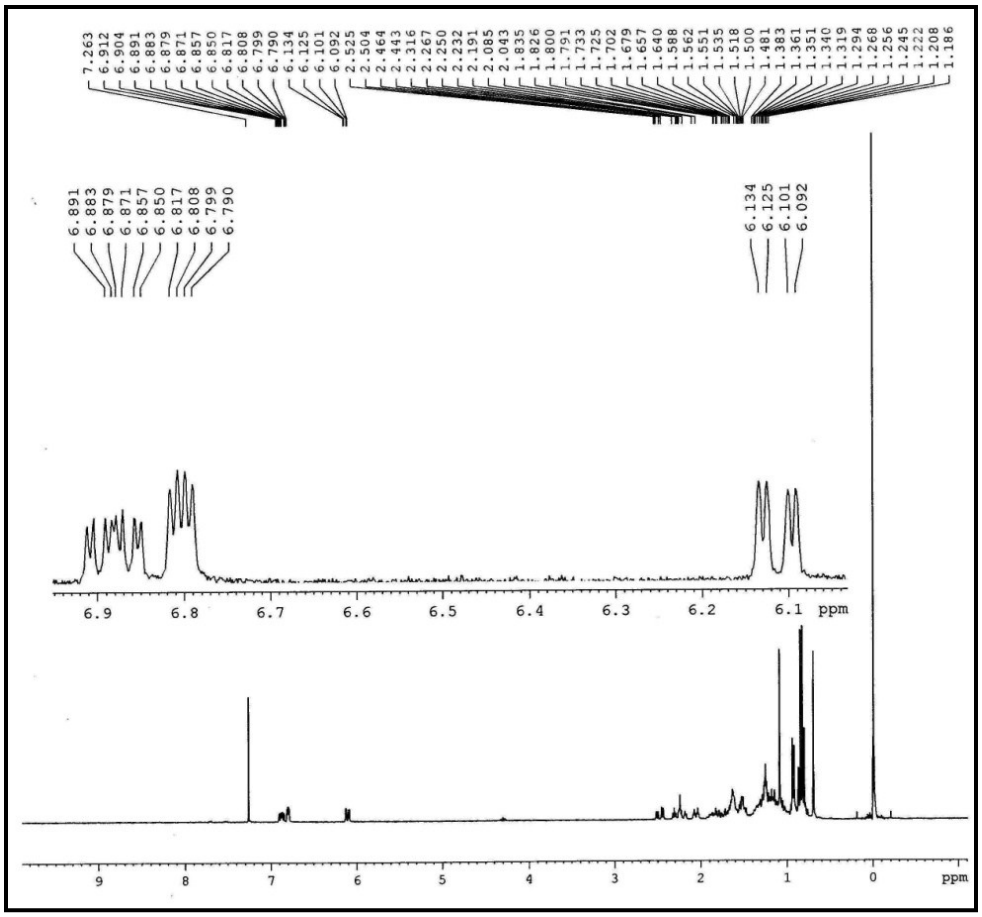


Figure S40. ^{1}H NMR spectrum (partially expanded) of stigmast-3,5-en-7-one (**10**).

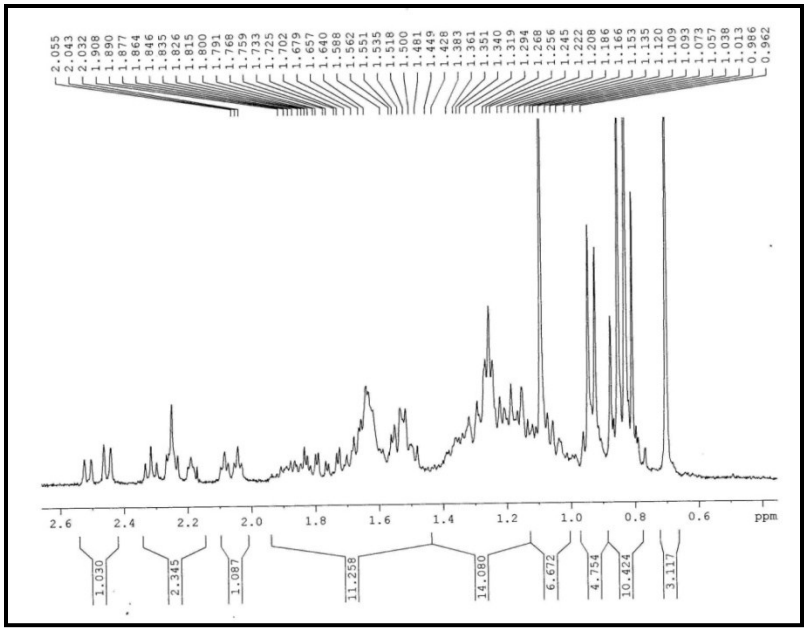


Figure S41. Partial ^{1}H NMR spectrum of stigmasta-3,5-diene-7-one (**10**).

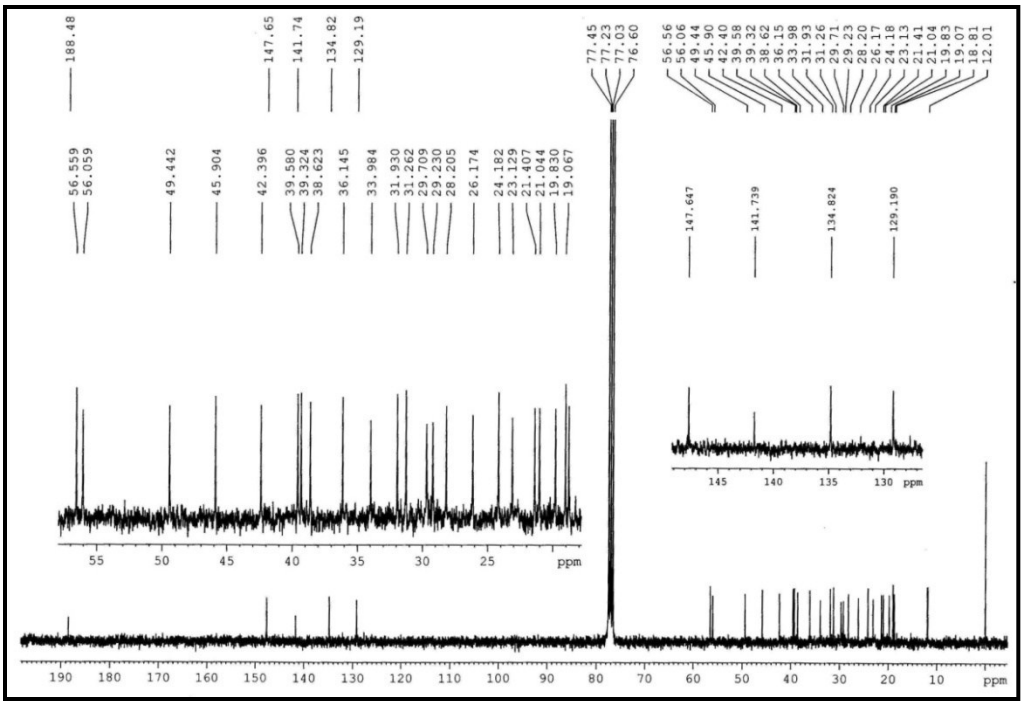


Figure S42. ^{13}C NMR spectrum of stigmasta-3,5-diene-7-one (**10**).

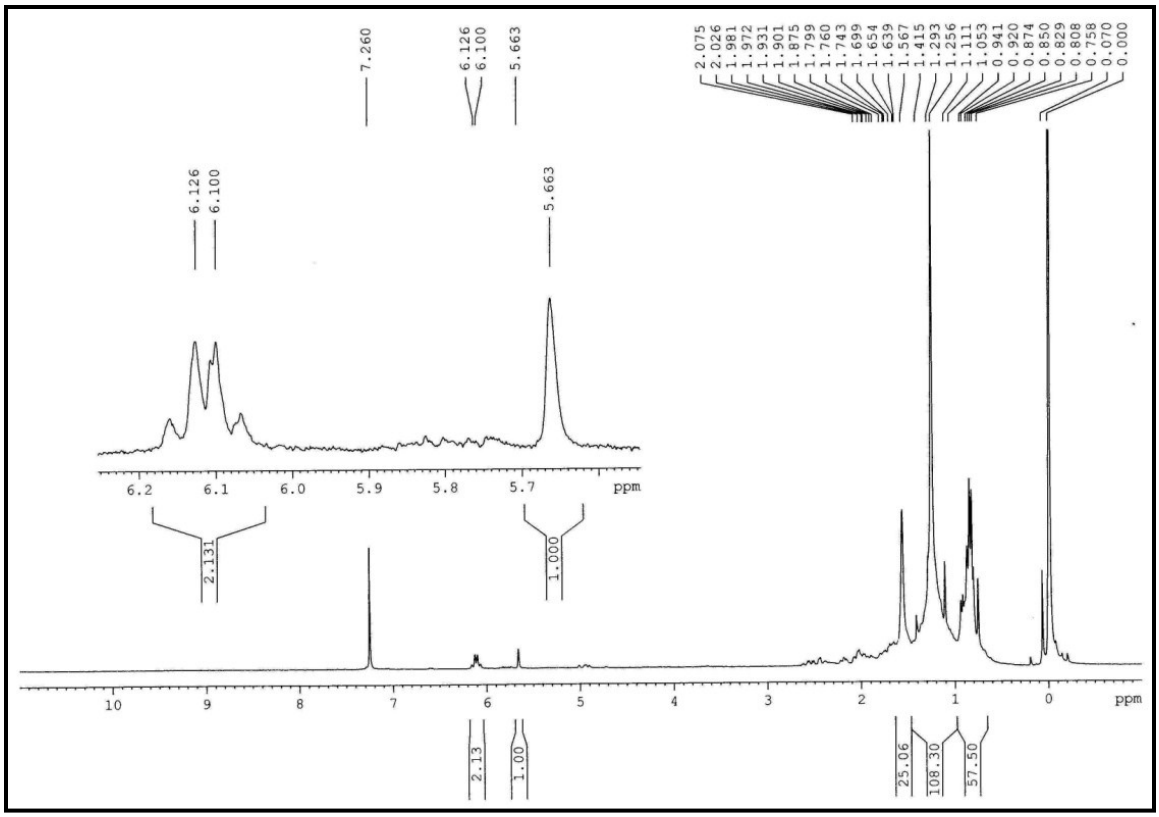


Figure S43. ^{1}H NMR spectrum (with partial expansion) of stigmasta-4,6-diene-3-one (**21**).

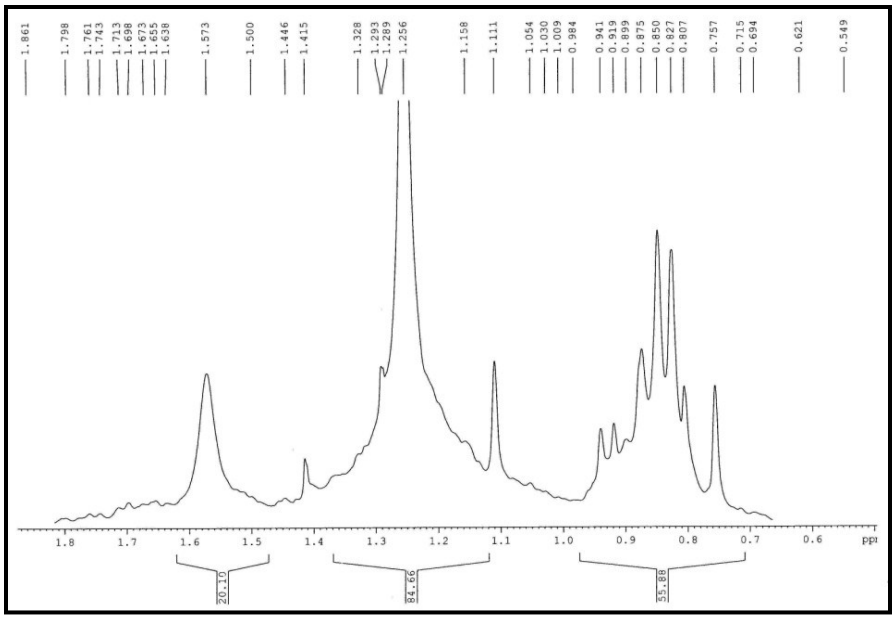


Figure S44. Partial ^{1}H NMR spectrum of stigmasta-4,6-diene-3-one (**21**).

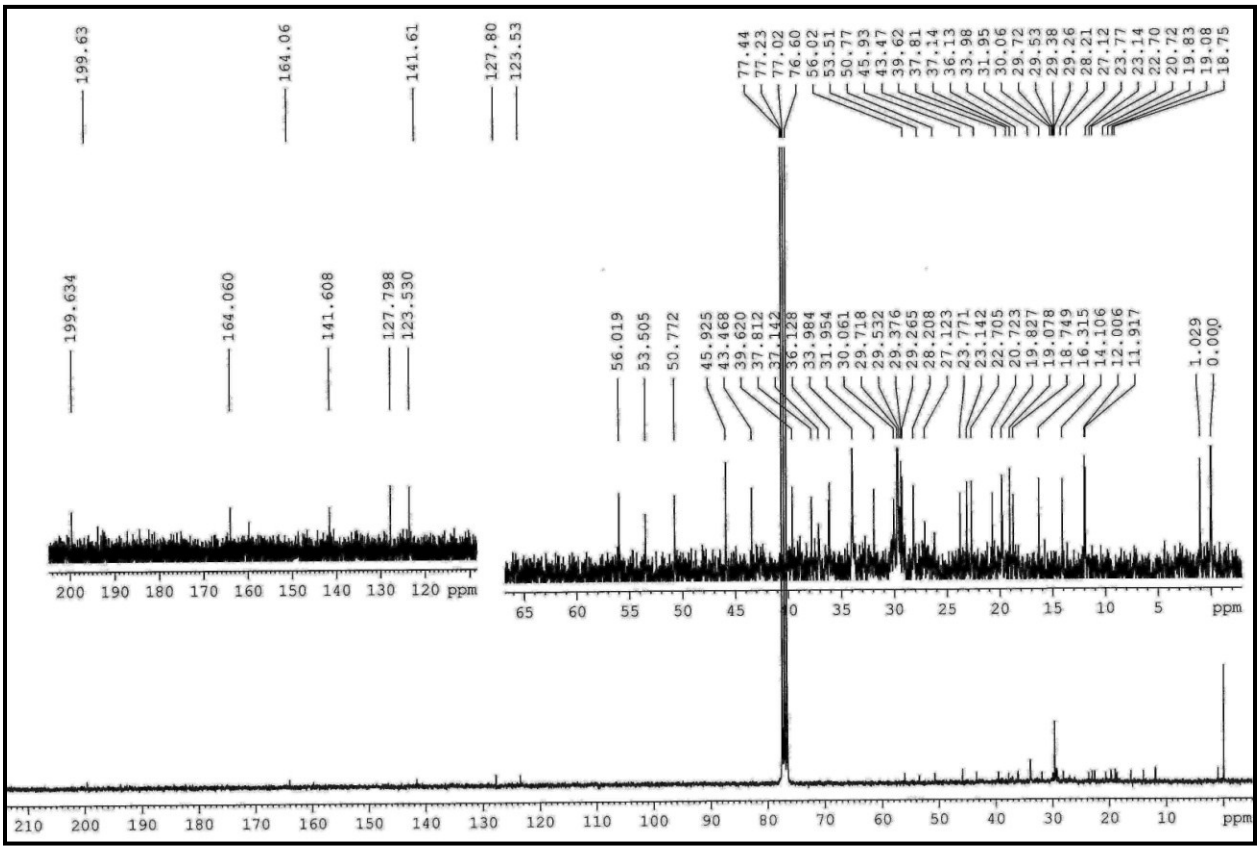


Figure S45. ^{13}C NMR spectrum of stigmasta-4,6-diene-3-one (**21**).

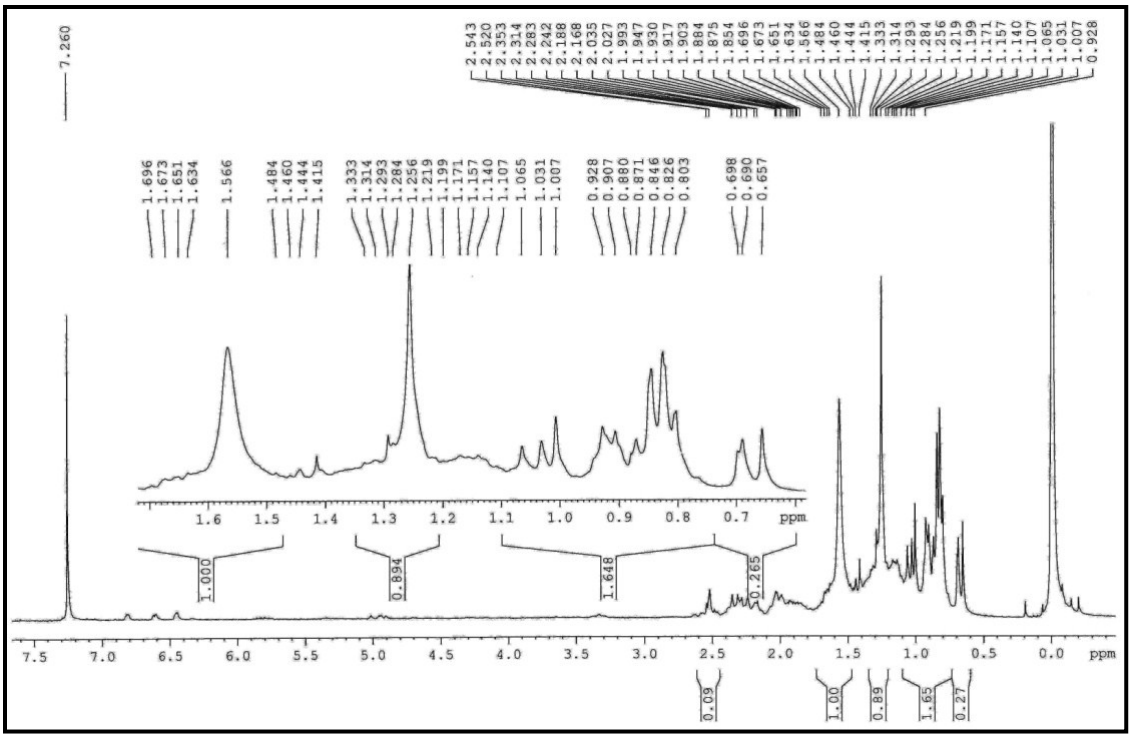


Figure S46. [1]H NMR spectrum of 5α-stigmastane-4,7-dione (**23**) (as mixture).

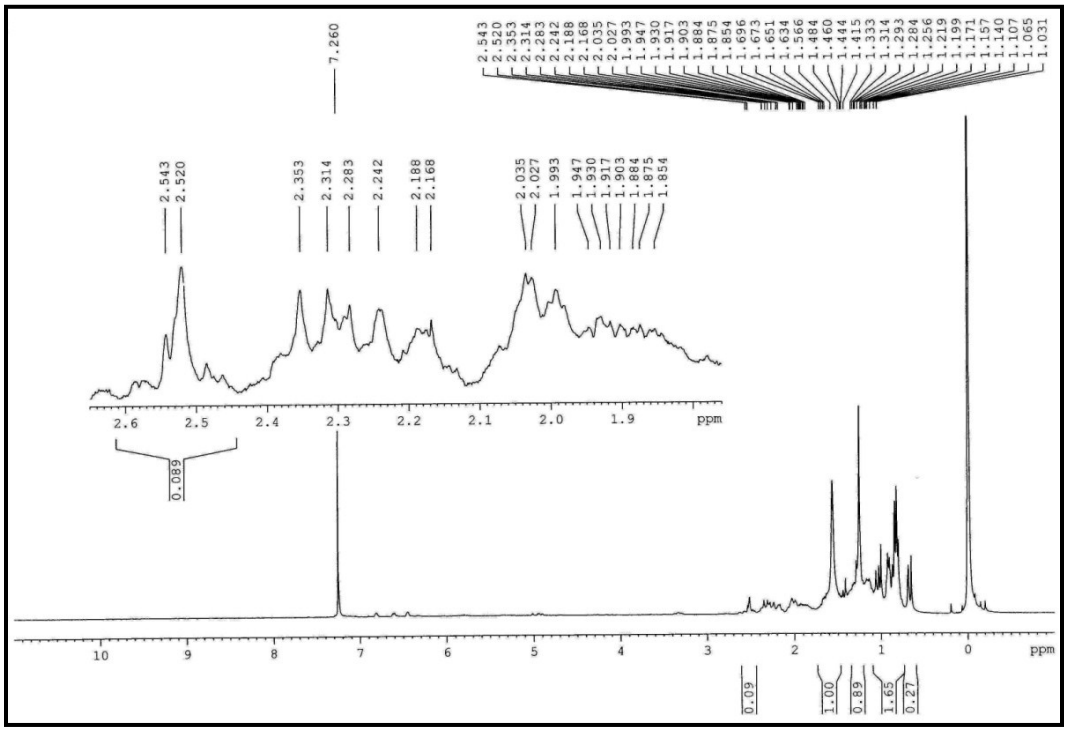


Figure S47. [1]H NMR spectrum (with partial expansion) of 5α-stigmastane-4,7-dione (**23**) (as mixture).

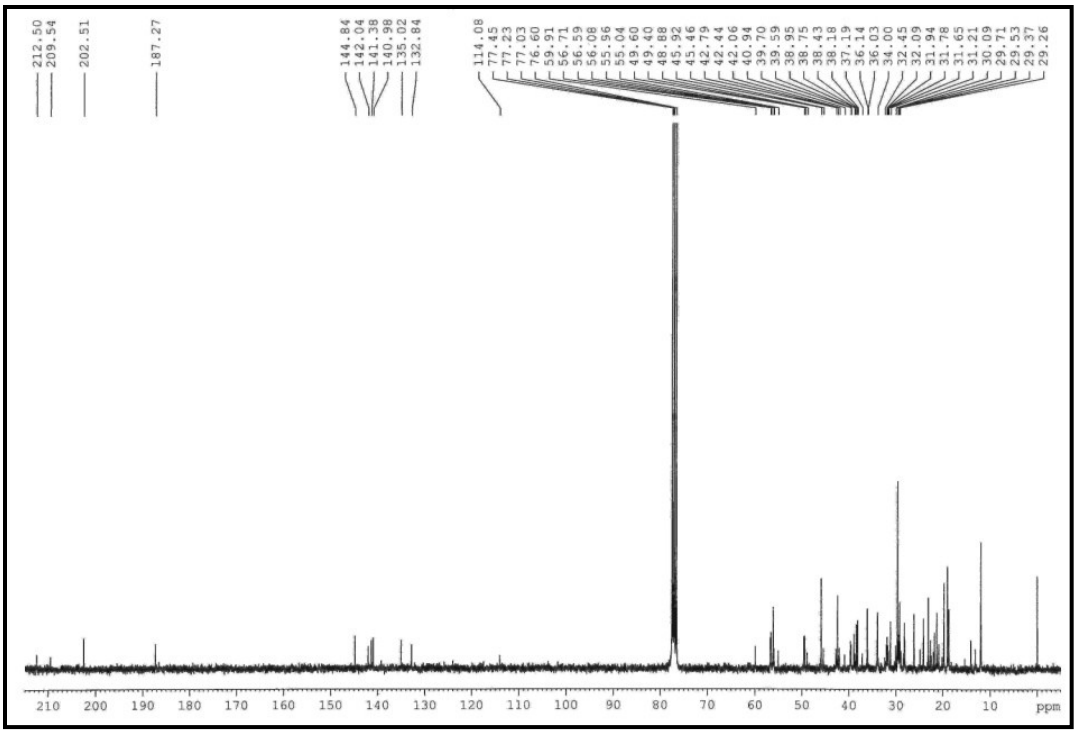


Figure S48. ^{13}C NMR spectrum of 5α-stigmastane-4,7-dione (**23**, as mixture).

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