Turk J Chem
34 (2010) , 359 – 366.

doi:10.3906/kim-0907-111

Convenient synthesis of monomeric steroids from steroidal oxalate dimers using flash vacuum pyrolysis (FVP)

Lutfun NAHAR[1,*], Alan B. TURNER[2] and Satyajit D. SARKER[3]

[1] *Drug Discovery and Design Research Division, Department of Pharmacy, School of Applied Sciences, University of Wolverhampton, MA Building, Wulfruna Street, Wolverhampton WV1 1LY, England, UK*
e-mail: L.Nahar@wlv.ac.uk

[2] *Japp Laboratory, Department of Chemistry, University of Aberdeen, Aberdeen AB24 3UE, Scotland, UK*

[3] *Department of Pharmacy, School of Applied Sciences, University of Wolverhampton, MM Building, Molineux Street, Wolverhampton WV1 1SB, England, UK*

Received 10.07.2009

Flash vacuum pyrolysis (FVP) or thermolysis (FVT), an environmentally friendly method for studying organic reaction mechanisms as well as synthesis, was applied to a series of oxalate dimers (**1**, **3**, **5**, **7**, **9**, **11**, **13**, and **15)** to synthesise monomeric enes, dienes, and a triene (**2**, **4**, **6**, **8**, **10**, **12**, **14**, and **16)**. All steroidal monomers were identified by spectroscopic means.

Key Words: Steroid, oxalate dimers, steroidal alkene, diene, triene, FVP.

Introduction

Flash vacuum pyrolysis (FVP) or thermolysis (FVT) is an environmentally friendly method for studying organic reaction mechanisms as well as synthesis. It generates unimolecular radical reactions that are not generally observed in conventional solution reactions.[1] The FVP of symmetrical oxalate of alcohols and phenols has attracted sporadic attention over the years.[2−9] The Trahanovsky group observed that the bibenzyl oxalates

*Corresponding author

readily gave bibenzyls,[2] whereas substrates containing β-hydrogens suffered elimination,[3,4] as did dialkyl oxalates in the liquid phase.[5,6] McNab[7] studied the mechanism of thermolysis of a fluorene oxalate, and smoking compositions containing oxalate ester flavorant-release additives were patented.[8] Pyrolysis has also been utilised as an analytical technique for sterol esters.[9]

Alkenes containing one or more double bonds are an important group of compounds, as they serve as feedstocks for the petrochemical industry. They are conveniently used to synthesise a wide range of compounds via simple addition reactions. The FVP techniques have been widely applied for synthesis of olefinic compounds. As part of our ongoing studies on synthesis and reactions of steroidal dimers, we report here the FVP studies on a series of steroidal oxalate dimers.[10–12]

Experimental

The starting materials, oxalate dimers, [bis (androst-4-en-3-on)-17β-yl oxalate (**1**), bis (5α-androstan-3-on)-17β-yl oxalate (**3**), bis (androst-5-en-17-on)-3β-yl oxalate (**5**), bis (pregn-5-en-20-on)-3β-yl-oxalate (**7**), bis-(5β-Cholan-24-oic acid methyl ester)-3α-yl oxalate (**9**), bis (cholest-5-en)-3β-yl oxalate (**11**), bis (5α-cholestan)-3β-yl oxalate (**13**), and bis (stigmasta-5,22t-dien)-3β-yl oxalate (**15**)] were synthesised and identified previously in our lab.[10–12] Melting points of the products were determined on a Gallenkamp melting point apparatus. Infrared spectra (wave numbers in cm^{-1}) were recorded on an ATI Mattson Genesis FTIR spectrophotometer as KBr pellets. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian Unity INOVA 400 MHz NMR spectrometer. Mass spectroscopic analyses were performed at the EPSRC Mass Spectrometry Service at Swansea.

General procedure for the flash vacuum pyrolysis (FVP) of oxalate dimers. The furnace was heated to 600 °C. A small quantity of oxalate dimer (20 mg) in a small round bottom flask was placed in the head of the apparatus and the system was evacuated to 10^{-2} mbar. The cold trap was cooled with liquid N_2 and the head was heated to 300 °C. Over a period of 1 h all the oxalate had sublimed. The liquid N_2 bath was removed and the system was opened to the atmosphere. The crude pyrolysate was washed out of the trap with the use of a small amount of $CHCl_3$ or DCM and EtOH. The solvent was evaporated to obtain the product and the crude residue was purified by preparative thin layer chromatography (PTLC) using 15%-20% EtOAc in a pet-ether (40-60 °C) solvent system.

Androsta-4,16-dien-3-one (2). The title compound (**2**, 5 mg, 29%) was obtained as a white solid, mp: 128-129 °C (lit. mp[13] 127-129.5 °C; IR[13]; MS[14] and ^{1}H-NMR[13]). ^{13}C-NMR (62.5 MHz, $CDCl_3$): δ 35.8 (C-1), 33.9 (C-2), 199.5 (C-3), 124.2 (C-4), 170.5 (C-5), 32.8 (C-6), 31.5 (C-7), 35.4 (C-8), 53.8 (C-9), 38.6 (C-10), 20.7 (C-11), 36.6 (C-12), 42.7 (C-13), 50.3 (C-14), 28.6 (C-15), 129.3 (C-16), 143.8 (C-17), 17.1 (C-18), 11.6 (C-19). ESIMS m/z: 271 $[M+H]^+$.

5α-Androst-16-en-3-one (4). The title compound (**4**, 5.5 mg, 32%) was obtained as a colourless solid, mp: 141-142 °C (lit. mp[13]: 140-141 °C; MS[15]; ^{1}H- and ^{13}C-NMR[16]). IR ($CHCl_3$): ν_{max} cm^{-1} 2964s (C-H), 2913s (C-H), 2854s (C-H), 1710s (ketonic C=O), 1628w (C=C), 1450m, 1414m, 1261m, 1068s, 1033s and 800m. ESIMS m/z: 273 $[M+H]^+$.

Androsta-3,5-dien-17-one (6). The crude product was subjected to PTLC (20% EtOAc in pet-ether) to obtain the title compound **6** (5 mg, 39%) as a white solid, mp: 88-89 °C (lit. mp[17]: 87-88 °C; MS[18]; UV[17];

^{1}H- and ^{13}C-NMR[17]). IR ($CHCl_3$): ν_{max} cm^{-1} 2965s (C-H), 2926s (C-H), 2852s (C-H), 1732s (ketonic C=O), 1637w (C=C), 1627w (C=C), 1444m, 1338m, 1311s, 1260s, 1188s, 1088s, 1020s and 809s. ESIMS m/z: 271 $[M+H]^+$.

Pregna-3,5-dien-20-one (8). The crude product was purified by PTLC (20% EtOAc in pet-ether) and the title compound **8** (5.5 mg, 32%) was obtained as a colourless solid, mp: 137-138 °C (lit. mp[19]: 138-141 °C; UV[19]; MS[20]; ^{1}H- and ^{13}C-NMR[20]). IR ($CHCl_3$): ν_{max} cm^{-1} 2962s (C-H), 2858s (C-H), 1703s (ketonic C=O), 1651w (C=C), 1637w (C=C), 1628w (C=C), 1497m, 1399m, 1260s, 1091s, 1018s and 799s. ESIMS m/z: 299 $[M+H]^+$.

5β-Cholan-3-en-24-oic acid methyl ester (10). PTLC (20% EtOAc in pet-ether) of the crude product yielded the title compound **10** (5.3 mg, 30%) as a white solid, mp: 72-73 °C (lit. mp[21]: 74.5-75 °C and ^{1}H-NMR[22]). IR ($CHCl_3$): ν_{max} cm^{-1} 2954s (C-H), 2936s (C-H), 2873s (C-H), 1735s (ester C=O), 1637w (C=C), 1560w (C=C), 1497m, 1399m, 1260s, 1091s, 1018s and 799s. ^{13}C-NMR (62.5 MHz, $CDCl_3$): δ 35.9 (C-1), 35.3 (C-2), 127.6 (C-3), 125.0 (C-4), 43.5 (C-5), 27.7 (C-6), 26.3 (C-7), 35.9 (C-8), 40.3 (C-9), 34.1 (C-10), 21.5 (C-11), 40.1 (C-12), 42.7 (C-13), 56.6 (C-14), 24.2 (C-15), 28.2 (C-16), 56.0 (C-17), 12.0 (C-18), 23.3 (C-19), 35.4 (C-20), 18.3 (C-21), 31.1 (C-22), 31.0 (C-23), 174.8 (C-24), 51.5 (24-OMe). ESIMS m/z: 373 $[M+H]^+$.

Cholesta-3,5-diene (12). The crude product was subjected to PTLC (15% EtOAc in pet-ether) to obtain the title compound **12** (5.9 mg, 33%) as a colourless solid, mp: 77-78 °C (lit. mp[23]: 77-78.5 °C; UV and MS[24]; ^{1}H- and ^{13}C-NMR[16]). IR ($CHCl_3$): ν_{max} cm^{-1} 2964s (C-H), 2934s (C-H), 2852s (C-H), 1655w (C=C), 1638w (C=C), 1467m, 1378m, 1261s, 1090s, 1035s and 800s. ESIMS m/z: 369 $[M+H]^+$.

5α-Cholest-2-ene (14). PTLC (15% EtOAc in pet-ether) of the crude product yielded the title compound **14** (5.5 mg, 31%) as a white solid, mp: 68-69 °C (lit.[25] mp: 65-68 °C and IR; UV[25]; MS[26]; ^{1}H- and ^{13}C-NMR[26]). ESIMS m/z: 371 $[M+H]^+$.

Stigmasta-3,5,22t-triene (16). The crude was purified by PTLC (15% EtOAc in pet-ether) and the title compound **16** (5.8 mg, 32%) was obtained as a colourless solid, mp: 109-110 °C, white solid (lit.[27] mp: 111-112 °C). IR ($CHCl_3$): ν_{max} cm^{-1} 2962s (C-H), 2922s (C-H), 2858m (C-H), 1655w (C=C), 1637w (C=C), 1458w, 1261s and 799s; UV[27]; ^{1}H- and ^{13}C-NMR (Table). ESIMS m/z: 395 $[M+H]^+$.

Results and discussion

All steroidal oxalate dimers (**1**, **3**, **5**, **7**, **9, 11**, **13** and **15**) were pyrolysed over 1 h at 600 °C and 10^{-2} mbar pressure (Schemes 1-8). All monomeric steroid enes, dienes, and triene (**2**, **4**, **6**, **8**, **10**, **12** and **14**), except **16**, were identified by comparison of their mp, IR, and NMR data with respective literature data. Compound **16** was identified by independent spectral analysis.

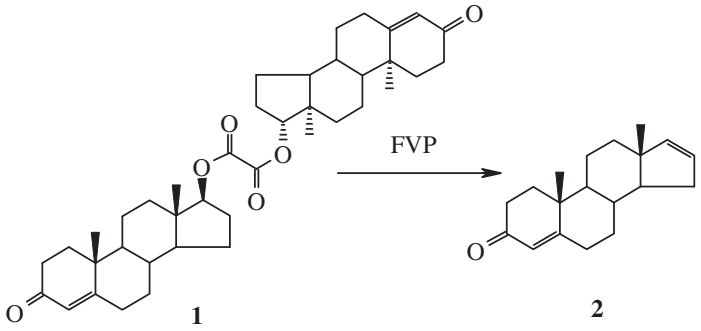
The FVP on dimers offered a good synthetic procedure for the generation of double bonds in all cases. These types of pyrolytic conversion take place via elimination of the CO_2 from the oxalate functionality and form a diradical intermediate, which then convert to form new double bonds. The possible reaction mechanism for the formation of a double bond via radical is shown in Scheme 9. In the intermediate step, the oxalate linkage was broken homolytically and radicals were formed. Then the alkyl radicals were formed via decarboxylation.

Generation of another new radical and extrusion of the hydrogen gas led to the formation of the double bond at Δ^3.

Table. ^{1}H- (coupling constant J in Hz in parentheses)^a and ^{13}C-NMR^b data of compound **16**.

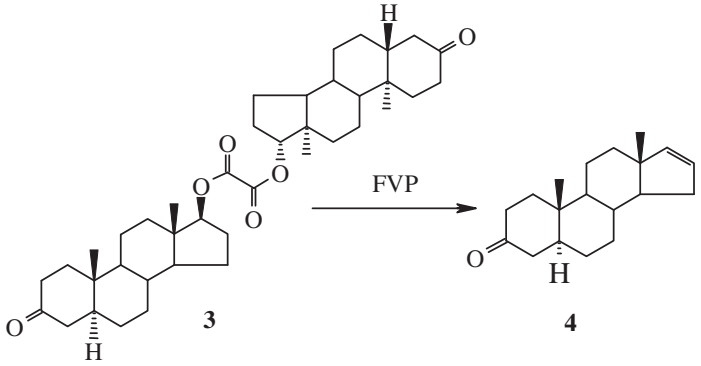
No.	Chemical shifts (δ) in ppm		No	Chemical shifts (δ) in ppm	
	^{1}H	^{13}C		^{1}H	^{13}C
1	0.95-2.30^c	35.5	16	0.95-2.30^c	29.2
2	0.95-2.30^c	23.3	17	0.95-2.30^c	56.3
3	5.60 br dt	129.3	18	0.72 s	12.5
4	5.92 br d	125.3	19	0.95 s	21.4
5	t	141.8	20	0.95-2.30^c	40.8
6	5.37 br t	123.4	21	1.00 d (6.1)	21.5
7	0.95-2.30^c	32.0	22	5.12 dd (8.5, 5.1)	138.6
8	0.95-2.30^c	32.2	23	4.98 dd (8.5, 5.1)	129.6
9	0.95-2.30^c	51.5	24	0.95-2.30^c	48.7
10	t	34.1	25	0.95-2.30^c	32.1
11	0.95-2.30^c	21.2	26	0.80 d (5.5)	19.3
12	0.95-2.30^c	40.0	27	0.80 d (5.5)	21.1
13	t	42.7	28	0.95-2.30^c	25.7
14	0.95 – 2.30^c	57.4	29	0.83 t (5.5)	12.5
15	0.95 – 2.30^c	24.5	t	t	t

^{a}Spectrum obtained in $CDCl_3$, 400 MHz; ^{b}Spectrum obtained in $CDCl_3$, 100 MHz; ^{c}Overlapped peaks within the region of δ 0.90 to 3.00 ppm

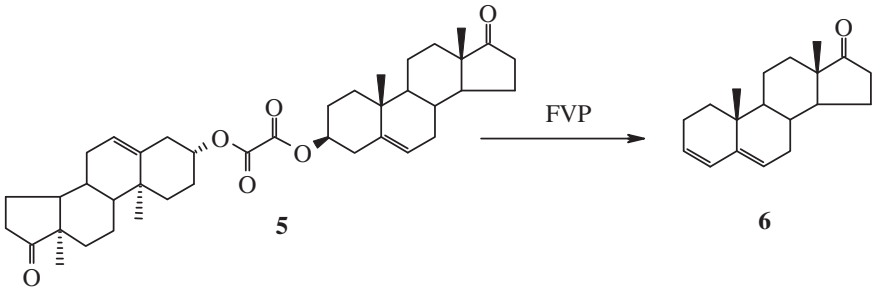


Scheme 1. The FVP of testosterone oxalate dimer (**1**).

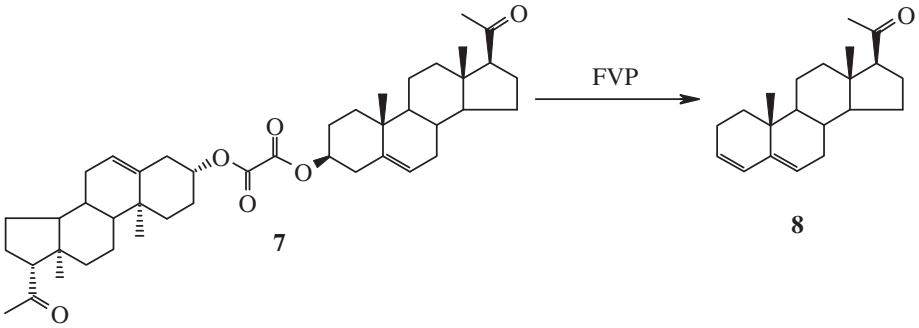
FVP of the testosterone oxalate dimer (**1**) afforded steroid diene, androsta-4,16-dien-3-one (**2**)[13,14] (Scheme 1). 5α-Androst-16-en-3-one (**4**)[13,15,16] was obtained from 5α-testosterone oxalate dimer (**3**) by pyrolysis (Scheme 2), and pyrolysis of dehydroandrostane (DHEA) oxalate dimer (**5**) produced monomeric steroid diene, androsta-3,5-dien-17-one (**6**)[17,18] (Scheme 3). Similar treatment of pregnenolone oxalate dimer (**7**) yielded pregna-3,5-dien-20-one (**8**) (Scheme 4).



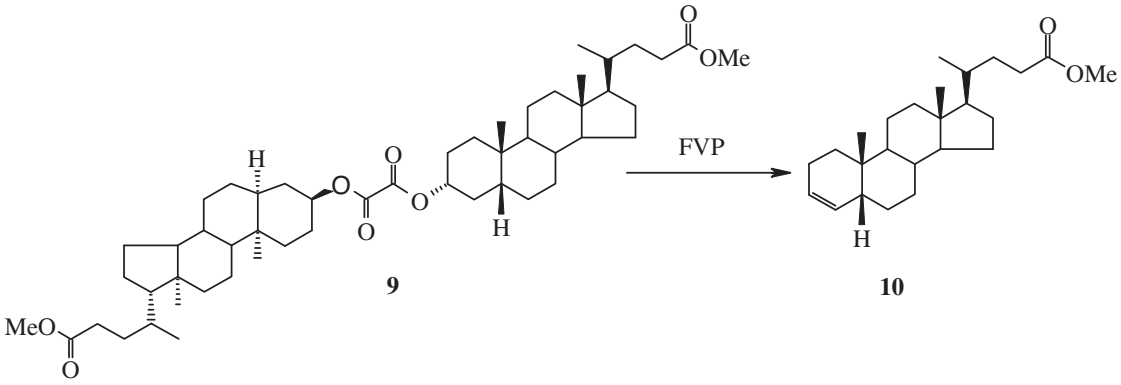
Scheme 2. The FVP of 5α-testosterone oxalate dimer (3).



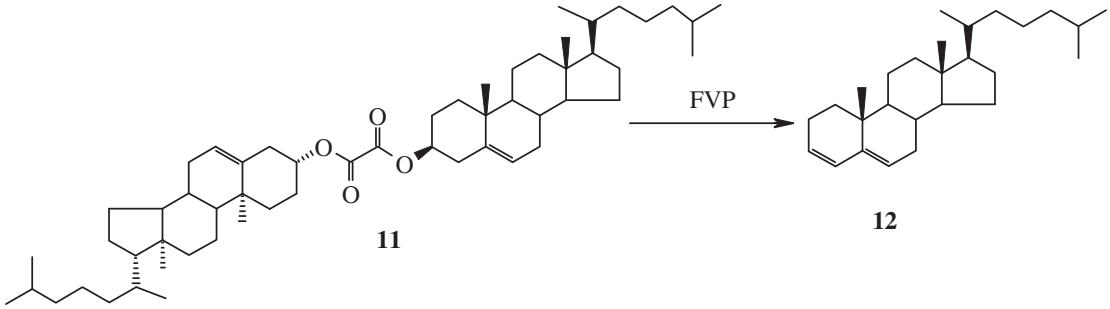
Scheme 3. The FVP of dehydroandrostane (DHEA) oxalate dimer (5).



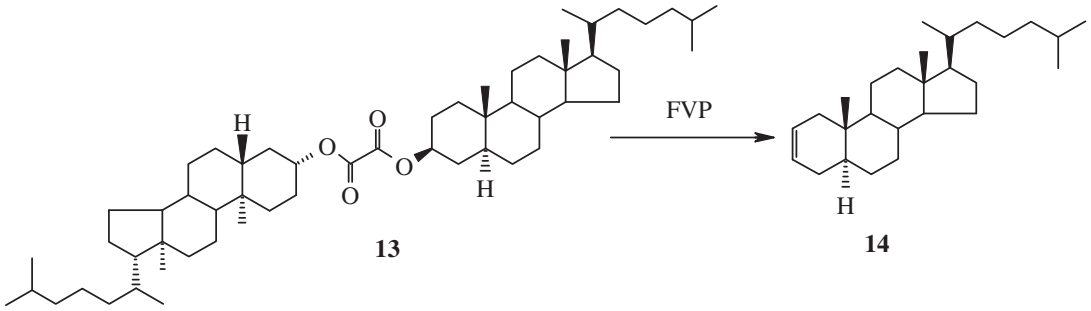
Scheme 4. The FVP of pregnenolone oxalate dimer (7).



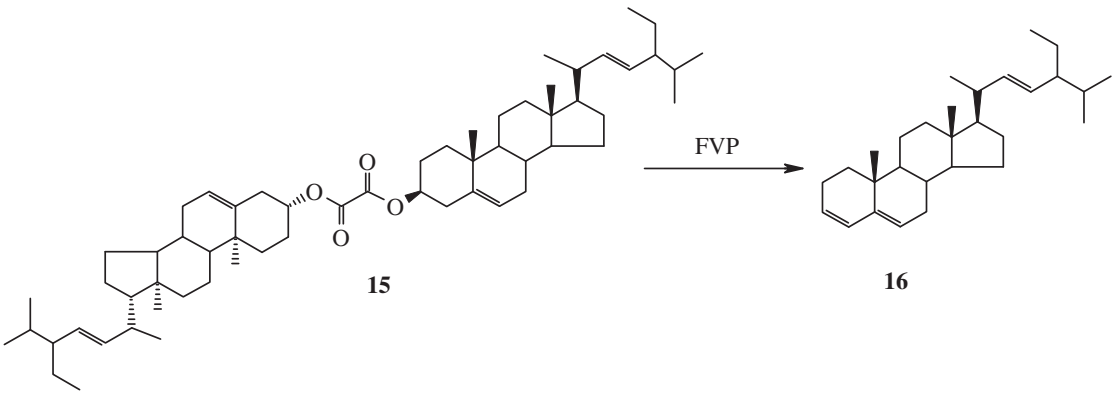
Scheme 5. The FVP of methyl lithocholate oxalate dimer (**9**).



Scheme 6. The FVP of cholesterol oxalate dimer (**11**).

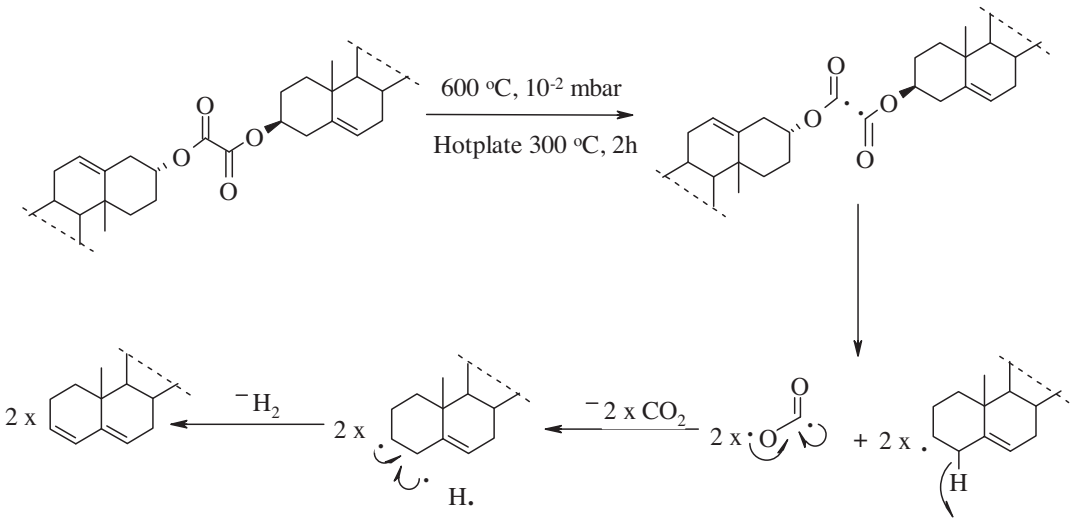


Scheme 7. The FVP of cholestane oxalate dimer (**13**).



Scheme 8. The FVP of stigmasterol oxalate dimer (**15**).

The FVP of methyl lithocholate oxalate dimer (**9**) and cholesterol oxalate dimer (**11**) resulted in the synthesis of, respectively, 5β-chol-3-en-24-oic acid methyl ester (**10**)[21,22] (Scheme 5) and cholesta-3,5-diene (**12**)[16,23,24] (Scheme 6). 5α-Cholest-2-ene (**14**)[25,26] was obtained from the pyrolysis of the cholestane oxalate dimer (**13**) (Scheme 7). Interestingly, it was found that, in the case of dimer **9**, solely 5β-cholan-3-en-24-oic acid methyl ester (**10**) was formed, whereas, in the case of dimer **13**, 90% 5α-cholest-2-ene (**14**) and also a small amount of 5α-cholest-3-ene were produced.



Scheme 9. Possible reaction mechanism for the formation of a double bond via radical.

The FVP of the stigmasterol oxalate dimer (**15**) yielded the monomer stigmasta-3,5,22*t*-triene (**16**) (Scheme 8). Compound **16** was identified primarily by comparing its mp and UV data with literature values.[27] The ESIMS spectrum of **16** displayed the *pseudo*molecular ion $[M+H]^+$ at m/z395. The IR spectrum showed absorption bands at 1655 and 1637 cm^{-1}, providing evidence for the presence of the double bonds in the molecule. The ^{1}H-NMR spectrum of compound **16** (Table) was similar to that of stigmasterol[16] with the exception that, instead of the signal for the C-3 oxymethine proton (as in stigmasterol), signals (δ 5.60 and 5.92) for an extra pair of olefinic protons (H-3 and H-4) were observed. The ^{13}C-NMR spectrum (Table) confirmed further the presence of the extra double bond between C-3 and C-4.

The FVP studies on oxalate dimers (1, 3, 5, 7, 9, 11, 13 and 15) established a convenient and environmentally friendly (as no reaction reagents were involved) one-step synthetic route for the synthesis of steroidal enes, dienes, and triene (2, 4, 6, 8, 10, 12, 14, and 16) for the first time.

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