Synthesis and Reactions of Some New Substituted Androstanopyrazoline and Androstanoisoxazole Derivatives Using Their Arylmethylene as Starting Materials

Mohamed M Abdulla[1], Abd El-Galil E Amr[2,3,]*, Mohamed A Al-Omar[2], Azza A Hussain[4], Mohamed S Amer[4]

[1]Research Unit, Saco Pharm. Co., 6th October City 11632, Egypt
[2] Pharmaceutical Chemistry Department, College of Pharmacy, King Saud University, Riyadh 11451, Saudi Arabia
[3]Applied Organic Chemistry Department, National Research Center, Dokki, Cairo, Egypt
[4] Chemistry Department, Faculty of Science, Zagazige University, Zagazige Egypt
aeamr1963@yahoo.com

Abstract. A series of substituted androstanopyrazoline and androstanoisoxazoleand their derivatives **3-13** have been prepared via the reacting of protected arylmethylene of 3β-hydroxy-androstan-17-one derivatives **2a-e** with hydrazine derivatives to yield N-substituted pyrazolines**3a-c, 4a-c** and**5a-c**, respectively. Coupling of **1d,e** with hydroxylamine hydrochloride to give oxazole derivatives **6a,b,** which was protected with acetyl chloride or trifluoroacetic anhydride to give protected products **7a,b** and **8a,b**. Additionally, the reaction of **1a,b,d** with diethyl malonate afforded diester derivatives **9a-c**. Also, treatment of **1c,d** with Adams catalyst gave decarbonyl derivatives **10a,b**, which was oxidized with potassium chromate in sulfuric acid to give the corresponding oxidized products **11a,b**.Finally, compounds **10a,b** was treated with acetyl chloride or trifluoroacetic anhydride to give protected products **12a,b** and **13a,b**.

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1. Introduction

In a previous work, we found that certain substituted steroidal and heterocyclic derivatives have been synthesized and used as androgenic, anabolic, and anti-inflammatory activities (Amr, et al., 2002; 2006), antiparkinsonian(Amr, et al., 2003; Al-Harbi, et al., 2013), antitumor (Amr, et al., 2004; Hernández-Vázquez, et al., 2013; Stringer, et al., 2013), antimicrobial (Amr, et al., 2003; Mandawad, et al., 2013; Zampieri, et al., 2008), and anti-inflammatory (de Oliveira, et al., 2012; Peng, et al., 2012) agents. Some of the steroidal compounds which were fused with different heterocyclic rings are an interesting in pharmacological properties, such as 5α-reductase and aromatase inhibitors, anti-inflammatory, and analgesic agents (Hukki, et al., 1968; Jung, et al., 2005). These derivatives are also well known for their pronounced anti-inflammatory properties (Bansal, et al., 2001; Bhat, et al., 1998) and are used as potent anti-diabetic agents (Ahn, et al., 2004; Villhauer, et al., 2002). Recently, some new heterocyclic compounds containing steroid moieties have been synthesized and used as 5α-reductase inhibitors, antiviral and anti-tumor(Al-Mohize, et al., 2012), aromatase and quinone reductase-2 inhibitors (Abdalla, et al., 2012), anti-Alzheimer (Abdalla, et al., 2012), anti-HIV-1, anti-HSV-1 (Khalifa, et al., 2013), antiparkinsonian (Bakhashwan, et al., 2012)and ant-arthritic, immune-suppressive (Alanazi, et al., 2013) agents [19-24]. In view of these reports and in continuation of our previous work in heterocyclic chemistry, we have synthesized some new compounds containing oxazole ring fused with steroidal structure for the evaluation of androgenic-anabolic activities in the future.

2. Experimental

All melting points are uncorrected and were measured using an Electrothermal capillary melting point apparatus. The IR spectra were recorded on a Shimadzu FT-IR 8101 PC infrared spectrophotometer. The ^{1}H- and ^{13}C-NMR spectra were determined with Bruker AM-200 MHz spectrometer. The chemical shifts are expressed on the δ (ppm) scale using TMS as the standard reference. Mass spectra were recorded on Finnigan SSQ operating at 70 ev.. Elemental analysis determined on a Perkin Elmer 240 (microanalysis), Microanalysis Center, Cairo University, Cairo, Egypt.

Synthesis of 1`-substituted-1`H-5`-substituted phenyl-5α-androstan[17,16-c]pyrazoline-3β-yl-trifluoroacetate derivatives 3a-c, 4a-c and 5a-c

A mixture of the arylmethylene derivatives **2a-c** (4 mmol) and hydrazine derivatives (5 mmol), namely, acetyl, methyl or phenyl hydrazine in glacial acetic acid (15 ml) was refluxed for 5-7 h. The

reaction mixture was poured into ice water, the obtained solid was filtered off, washed with water, dried, and crystallized from the proper solvent to give N-substituted pyrazoline derivatives **3a-c, 4a-c** and **5a-c,** respectively.

1`-Acetyl-1`H-5`-(4-bromophenyl)-5α-androstan[17,16-c]pyrazoline-3β-yl-trifluoroacetate (3a).

Yield.86%, mp. 306-308°C, $[\alpha]_D^{25}$ = + 128 (c 1, $CHCl_3$); IR (KBr): 1758 (C=O), 1642 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.82, 0.92 (2s, 6H, $2CH_3$), 0.96-1.10 (m, 1H, CH), 1.21-1.88 (m, 14H, $7CH_2$), 2.02-2.06 (m, 1H, CH), 2.10 (s, 3H, $COCH_3$), 2.18-2.30 (m, 2H, CH_2), 2.36 (m, 1H, CH), 2.45 (m, 1H, C-H), 2.58 (m, 1H, 3α-CH), 3.05 (m, 1H, 5 α-CH), 3.25 (d, 1H, CH), 7.25-7.50 (m, 4H, Ar-H). MS (EI): m/z 610 [M^+, 15]. Anal. $C_{30}H_{36}BrF_3N_2O_3$ (609.52): Calcd C, 59.12; H, 5.95; N, 4.60; found C, 59.05; H, 5.90; N, 4.54.

1`-Acetyl-1`H-5`-(4-fluorophenyl)-5α-androstan[17,16-c]pyrazoline-3β-yl-trifluoroacetate (3b).

Yield.78%, mp. 218-220°C, $[\alpha]_D^{25}$ = + 168 (c 1, $CHCl_3$); IR (KBr): 1760 (C=O), 1636 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.85, 0.94 (2s, 6H, $2CH_3$), 0.98-1.10 (m, 1H, CH), 1.20-1.86 (m, 14H, $7CH_2$), 2.00 (m, 1H, CH), 2.12 (s, 3H, $COCH_3$), 2.21-2.30 (m, 2H, CH_2), 2.38 (m, 1H, CH), 2.45 (m, 1H, C-H), 2.56 (m, 1H, 3α-CH), 3.04 (m, 1H, 5 α-CH), 3.26 (d, 1H, CH), 7.20-7.50 (m, 4H, Ar-H). MS (EI): m/z % = 549 [M^+, 24]. Anal. $C_{30}H_{36}F_4N_2O_3$ (548.61): Calcd C, 65.68; H, 6.61; N, 5.11; found C, 65.60; H, 6.55; N, 5.06.

1`-Acetyl-1`H-5`-(4-methylphenyl)-5α-androstan[17,16-c]pyrazoline-3β-yl-trifluoroacetate (3c).

Yield.72%, mp. 305-307°C, $[\alpha]_D^{25}$ = + 168 (c 1, $CHCl_3$); IR (KBr): 1756 (C=O), 1640 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.83, 0.92 (2s, 6H, $2CH_3$), 0.96-1.10 (m, 1H, CH), 1.24-1.88 (m, 14H, $7CH_2$), 2.06 (m, 1H, CH), 2.10 (s, 3H, $COCH_3$), 2.18-2.30 (m, 5H, CH_2 + CH_3), 2.36 (m, 1H, CH), 2.45 (m, 1H, C-H), 2.58 (m, 1H, 3α-CH), 3.05 (m, 1H, 5 α-CH), 3.25 (d, 1H, CH), 7.25-7.50 (m, 4H, Ar-H). MS (EI): m/z % = 545 [M^+, 16]. Anal. $C_{31}H_{39}F_3N_2O_3$ (544.65): Calcd C, 68.36; H, 7.22; N, 5.14; found C, 68.30; H, 7.16; N, 5.10.

1`-Phenyl-1`H-5`-(4-bromophenyl)-5α-androstan[17,16-c]pyrazoline-3β-yl-trifluoroacetate (4a).

Yield.84%, mp. 310-312°C, $[\alpha]_D^{25}$ = + 158 (c 1, $CHCl_3$); IR (KBr): 1755 (C=O), 1638 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.83, 94 (2s, 6H, $2CH_3$), 0.95-1.12 (m, 1H, CH), 1.18-1.87 (m, 14H, $7CH_2$), 2.08 (m, 1H, CH), 2.18-2.30 (m, 2H, CH_2), 2.35 (m, 1H, CH), 2.45 (m, 1H, C-H), 2.58 (m, 1H, 3α-CH), 3.12 (m, 1H, 5 α-CH), 3.24 (d, 1H, CH), 7.22-7.62 (m, 9H, Ar-H). MS (EI): m/z % = 644 [M^+, 28]. Anal. $C_{34}H_{38}BrF_3N_2O_2$ (643.58): Calcd C, 63.45; H, 5.95; N, 4.35; found C, 63.40; H, 5.90; N, 4.30.

1`-Phenyl-1`H-5`-(4-fluorophenyl)-5α-androstan[17,16-c]pyrazoline-3β-yl-trifluoroacetate (4b).

Yield.45%, mp. 228-230°C, $[\alpha]_D^{25}$ = + 168 (c 1, $CHCl_3$); IR (KBr): 1756 (C=O), 1632 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.84, 0.96 (2s, 6H, $2CH_3$), 0.99-1.13 (m, 1H, CH), 1.20-1.90 (m, 14H, $7CH_2$), 2.01 (m, 1H, CH), 2.21-2.32 (m, 2H, CH_2), 2.38 (m, 1H, CH), 2.44 (m, 1H, C-H), 2.56 (m, 1H, 3α-CH), 3.08 (m, 1H, 5 α-CH), 3.28 (d, 1H, CH), 7.15-7.58 (m, 9H, Ar-H). MS (EI): m/z % = 582 [M^+, 14]. Anal. $C_{34}H_{38}F_4N_2O_2$ (582.67): Calcd C, 70.08; H, 6.57; N, 4.81; found C, 70.00; H, 6.50; N, 4.75.

1`-Phenyl-1`H-5`-(4-methylphenyl)-5α-androstan[17,16-c]pyrazoline-3β-yl-trifluoroacetate (4c).

Yield.62%, mp. 292-294°C, $[\alpha]_D^{25}$ = + 136 (c 1, $CHCl_3$); IR (KBr): 1762 (C=O), 1635 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.86, 0.96 (2s, 6H, $2CH_3$), 0.99-1.10 (m, 1H, CH), 1.22-1.86 (m, 14H, $7CH_2$), 2.05 (m, 1H, CH), 2.18-2.30 (m, 5H, CH_2 + CH_3), 2.36 (m, 1H, CH), 2.45 (m, 1H, C-H), 2.58 (m, 1H, 3α-CH), 3.08 (m, 1H, 5 α-CH), 3.25 (d, 1H, CH), 7.12-7.55 (m, 9H, Ar-H). MS (EI): m/z 579 [M^+, 6]. Anal. $C_{35}H_{41}F_3N_2O_2$ (578.71): Calcd C, 72.64; H, 7.14; N, 4.84; found C, 72.60; H, 7.10; N, 4.80.

1`-Methyl-1`H-5`-(4-bromophenyl)-5α-androstan[17,16-c]pyrazoline-3β-yl-trifluoroacetate (5a).

Yield.82%, mp. 301-303°C, $[\alpha]_D^{25}$ = + 142 (c 1, $CHCl_3$); IR (KBr): 1758 (C=O), 1632 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.85, 0.98 (2s, 6H, $2CH_3$), 1.05-1.15 (m, 1H, CH), 1.19-1.88 (m, 14H, $7CH_2$), 2.08 (m, 1H, CH), 2.18-2.30 (m, 5H, CH_2+CH_3), 2.36 (m, 1H, CH), 2.45 (m, 1H, C-H), 2.58 (m, 1H, 3α-CH), 3.14 (m, 1H, 5 α-CH), 3.24 (d, 1H, CH), 7.22-7.62 (m, 4H, Ar-H). MS (EI): m/z % = 581 [M^+, 22]. Anal. $C_{29}H_{36}BrF_3N_2O_2$ (581.51): Calcd C, 59.90; H, 6.24; N, 4.82; found C, 59.82; H, 6.18; N, 4.75.

1`-Methyl-1`H-5`-(4-fluorophenyl)-5α-androstan[17,16-c]pyrazoline-3β-yl-trifluoroacetate (5b).

Yield.77%, mp. 316-318°C, $[\alpha]_D^{25}$ = + 136 (c 1, $CHCl_3$); IR (KBr): 1754 (C=O), 1628 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.85, 0.95 (2s, 6H, $2CH_3$), 0.99-1.15 (m, 1H, CH), 1.20-1.85 (m, 14H, $7CH_2$), 2.02 (m, 1H, CH), 2.20-2.34 (m, 5H, CH_2+CH_3), 2.40 (m,

1H, CH), 2.46 (m, 1H, C-H), 2.58 (m, 1H, 3α-CH), 3.08 (m, 1H, 5 α-CH), 3.26 (d, 1H, CH), 7.15-7.58 (m, 4H, Ar-H). MS (EI): m/z % = 521 [M^+, 16]. Anal. $C_{29}H_{36}F_4N_2O_2$ (520.60): Calcd C, 66.91; H, 6.97; N, 5.38; found C, 66.83; H, 6.93; N, 5.32.

1`-Methyl-1`H-5`-(4-methylphenyl)-5α-androstan[17,16-c]pyrazoline-3β-yl-trifluoroacetate (5c).

Yield.78%, mp. 248-250°C, $[\alpha]_D^{25}$ = + 118 (c 1, $CHCl_3$); IR (KBr): 1760 (C=O), 1630 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.88, 0.95 (2s, 6H, $2CH_3$), 0.98-1.10 (m, 1H, CH), 1.23-1.86 (m, 14H, $7CH_2$), 2.02 (m, 1H, CH), 2.18-2.35 (m, 8H, CH_2 + $2CH_3$), 2.38 (m, 1H, CH), 2.46 (m, 1H, C-H), 2.60 (m, 1H, 3α-CH), 3.06 (m, 1H, 5 α-CH), 3.24 (d, 1H, CH), 7.14-7.56 (m, 4H, Ar-H). MS (EI): m/z % = 517 [M^+, 30]. Anal. $C_{30}H_{39}F_3N_2O_2$ (516.64): Calcd C, 69.74; H, 7.61; N, 5.42; found C, 69.68; H, 7.55; N, 5.35.

Synthesis of 5`-(substituted phenyl-5α-androstan[17,16-c]isoxazole-3β-ol derivatives 6a,b

A mixture of the arylmethylene derivatives **1d,e** (10 mmol) and hydroxylamine hydrochloride (12 mmol) in sodium ethoxide [92 mg sodium metal in 25 ml absolute ethanol] was refluxed for 7 h. The reaction mixture was evaporated under reduced pressure. The obtained solid was washed with 10% HCl, filtered off, dried and crystallized from methyl acetate to give isoxazole derivatives **6a,b,** respectively.

5`-(Phenyl)-5α-androstan[17,16-c]isoxazole-3β-ol (6a).

Yield.82%, mp. 276-278°C, $[\alpha]_D^{25}$ = + 109 (c 1, $CHCl_3$); IR (KBr): 3439 (OH), 3022 (CH, Ar), 2937 (CH, Aliph), 1614 (C=C), 1600 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.85, 0.95 (2s, 6H, $2CH_3$), 0.99-1.12 (m, 1H, CH), 1.18-1.88 (m, 14H, $7CH_2$), 2.02 (m, 1H, CH), 2.16-2.30 (m, 2H, CH_2), 2.36 (m, 1H, CH), 2.45 (m, 1H, C-H), 2.58 (m, 1H, 3α-CH), 3.12 (m, 1H, 5 α-CH), 3.24 (d, 1H, CH), 7.20-7.62 (m, 5H, Ar-H), 10.25 (s, 1H, OH, exchangeable with D_2O). MS (EI): m/z % = 393 [M^+, 24]. Anal. C26H35NO2 (393.56): Calcd C, 79.35; H, 8.96; N, 3.56; found C, 79.30; H, 8.90; N, 3.50.

5`-(4-Methoxyphenyl)-5α-androstan[17,16-c]isoxazol-3β-ol (6b).

Yield.76%, mp. 276-278°C, $[\alpha]_D^{25}$ = + 98 (c 1, $CHCl_3$); IR (KBr): 3454 (OH), 3032 (CH, Ar), 2945 (CH, Aliph), 1616 (C=C), 1601 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.84, 0.95 (2s, 6H, $2CH_3$), 0.99-1.15 (m, 1H, CH), 1.20-1.87 (m, 14H, $7CH_2$), 2.01 (m, 1H, CH), 2.21-2.32 (m, 2H, CH_2), 2.38 (m, 1H, CH), 2.44 (m, 1H, C-H), 2.56 (m, 1H, 3α-CH), 3.08 (m, 1H, 5 α-CH), 3.28 (d, 1H, CH), 3.50 (s, 3H, OCH_3), 7.15-7.58 (m, 4H, Ar-H), 10.18 (s, 1H, OH, exchangeable with D_2O). MS (EI): m/z % = 423 [M^+, 14]. Anal. $C_{27}H_{37}NO_3$ (423.59): Calcd C, 76.56; H, 8.80; N, 3.31; found C, 76.50; H, 8.75; N, 3.25.

Synthesis of 5`-(substituted phenyl-5α-androstan[17,16-c]isoxazole-3β-yl-acetate derivatives 7a,b and 8a,b

A solution of **6a,b** (4 mmol) in acetyl chloride or trifluoroacetic anhydride (5 mL) was left overnight at room temperature. The reaction mixture was evaporated under reduced pressure. The obtained residue was washed with aqueous sodium carbonate, filtered off, dried and crystallized from acetone to give acetate isoxazole derivatives **7a,b**and **8a,b,** respectively.

5`-(Phenyl)-5α-androstan[17,16-c]isoxazole-3β-yl-acetate (7a).

Yield.65%, mp. 216-218°C, $[\alpha]_D^{25}$ = + 114 (c 1, $CHCl_3$); IR (KBr): 3076 (CH, Ar), 2932 (CH, Aliph), 1734 (C=O), 1612 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.83, 0.94 (2s, 6H, $2CH_3$), 0.99-1.14 (m, 1H, CH), 1.18-1.88 (m, 14H, $7CH_2$), 2.06 (m, 1H, CH), 2.09-2.24 (m, 5H, CH_2 + $COCH_3$), 2.32 (m, 1H, CH), 2.46 (m, 1H, C-H), 2.58 (m, 1H, 3α-CH), 3.12 (m, 1H, 5 α-CH), 3.32 (d, 1H, CH), 7.20-7.60 (m, 5H, Ar-H). MS (EI): m/z % = 436 [M^+, 21]. Anal. $C_{28}H_{37}NO_3$ (435.60): Calcd C, 77.20; H, 8.56; N, 3.22; found C, 77.12; H, 8.50; N, 3.16.

5`-(4-Methoxyphenyl)-5α-androstan[17,16-c]isoxazol-3β-yl-acetate (7b).

Yield.72%, mp. 232-234°C, $[\alpha]_D^{25}$ = + 109 (c 1, $CHCl_3$); IR (KBr): 3086 (CH, Ar), 2942 (CH, Aliph), 1732 (C=O), 1610 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.87, 0.95 (s, 3H, CH_3), 1.05-1.15 (m, 1H, CH), 1.22-1.89 (m, 14H, $7CH_2$), 2.05 (m, 1H, CH), 2.16-2.26 (m, 5H, CH_2+ $COCH_3$), 2.35 (m, 1H, CH), 2.45 (m, 1H, C-H), 2.55 (m, 1H, 3α-CH), 3.12 (m, 1H, 5 α-CH), 3.29 (d, 1H, CH), 3.48 (s, 3H, OCH_3), 7.12-7.60 (m, 4H, Ar-H). MS (EI): m/z % = 466 [M^+, 32]. Anal. $C_{29}H_{39}NO_4$ (465.62): Calcd C, 74.81; H, 8.44; N, 3.01; found C, 74.75; H, 8.40; N, 2.95.

5`-(Phenyl)-5α-androstan[17,16-c]isoxazole-3β-yl-trifluoroacetate (8a).

Yield.76%, mp. 266-268°C, $[\alpha]_D^{25}$ = + 156 (c 1, $CHCl_3$); IR (KBr): 3100 (CH, Ar), 2980 (CH, Aliph), 1735 (C=O), 1615 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.85, 0.96 (2s, 6H, $2CH_3$), 1.04-1.16 (m, 1H, CH), 1.22-1.85 (m, 14H, $7CH_2$), 2.03 (m, 1H, CH), 2.12-2.24 (m, 2H, CH_2), 2.35 (m, 1H, CH), 2.48 (m, 1H, C-H), 2.56 (m, 1H, 3α-CH), 3.14 (m, 1H, 5 α-CH), 3.35 (d, 1H, CH), 7.18-7.62 (m, 5H, Ar-H). MS (EI): m/z % = 490 [M^+, 40]. Anal. $C_{28}H_{34}F_3NO_3$ (489.57): Calcd C, 68.69; H, 7.00; N, 2.86; found C, 68.62; H, 6.94; N, 2.80.

5`-(4-Methoxyphenyl)-5α-androstan[17,16-c]isoxazol-3β-yl-trifluoroacetate (8b).

Yield 82%, mp. 286-288°C, $[\alpha]_D^{25}$ = + 167 (c 1, $CHCl_3$); IR (KBr): 3082 (CH, Ar), 2956 (CH, Aliph), 1737 (C=O), 1608 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.86, 0.97 (2s, 6H, $2CH_3$), 1.00-1.16 (m, 1H, CH), 1.20-1.88 (m, 14H, $7CH_2$), 2.04 (m, 1H, CH), 2.15-2.28 (m, 2H, CH_2), 2.36 (m, 1H, CH), 2.46 (m, 1H, C-H), 2.56 (m, 1H, 3α-CH), 3.14 (m, 1H, 5 α-CH), 3.30 (d, 1H, CH), 3.46 (s, 3H, OCH_3), 7.14-7.62 (m, 4H, Ar-H). MS (EI): m/z % = 420 [M^+, 24]. Anal. $C_{29}H_{36}F_3NO_4$ (519.60): Calcd C, 67.03; H, 6.98; N, 2.70; found C, 66.92; H, 6.93; N, 2.65.

Synthesis of 16-[(α-diethyl)malonyl)-substituted phenyl]-3β-hydroxyl-androstan-17-one 9a-c

A mixture of **1a,b,d** (10 mmol), diethyl malonate (10 mmol) in sodium ethoxide [920 mg of sodium metal in 25 ml of absolute ethanol] was refluxed for 4-6 h. The reaction mixture was evaporated under reduced pressure, the obtained residue was washed with 10% HCl, dried and purified by flash chromatographed on silica gel and eluted with toluene:ethyl acetate (36:3, v:v) to give diethyl ester derivatives **9a-c,** respectively.

16-[(α-Diethyl)malonyl)-phenyl]-3β-hydroxyl-androstan-17-one (9a).

Yield.42%, mp. 236-238°C, $[\alpha]_D^{25}$ = + 122 (c 1, $CHCl_3$); IR (KBr): 3650 (OH), 3066 (CH, Ar), 2950 (CH, Aliph), 1734 (C=O), 1628 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.82, 0.94 (2s, 6H, $2CH_3$), 0.98-1.14 (m, 1H, CH), 1.20-1.31 (m, 10H, $2CH_2$+$2CH_3$), 1.38-1.84 (m, 10H, $5CH_2$), 1.95 (m, 1H, CH), 2.20-2.35 (m, 2H, CH_2), 2.45 (t, 1H, CH), 2.51 (m, 1H, CH), 2.58 (m, 1H, 3α-CH), 3.18 (m, 1H, 5α-CH), 3.46 (d, 1H, CH), 4.00 (q, 4H, $2CH_2$), 4.20 (t, 1H, CH), 7.10-7.55 (m, 5H, Ar-H), 10.22 (s, 1H, OH, exchangeable with D_2O). MS (EI): m/z % = 539 [M^+, 18]. Anal. $C_{33}H_{46}O_6$ (538.71): Calcd C, 73.57; H, 8.61; found C, 73.50; H, 8.55.

16-[(α-Diethyl)malonyl)-4-bromophenyl]-3β-hydroxyl-androstan-17-one (9b).

Yield.44%, mp. 181-183°C, $[\alpha]_D^{25}$ = + 165 (c 1, $CHCl_3$); IR (KBr): 3654 (OH), 3070 (CH, Ar), 2955 (CH, Aliph), 1735 (C=O), 1618 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.84, 0.95 (2s, 6H, $2CH_3$), 0.98-1.12 (m, 1H, CH), 1.18-1.30 (m, 10H, $2CH_2$+$2CH_3$), 1.38-1.86 (m, 10H, $5CH_2$), 1.97 (m, 1H, CH), 2.20-2.35 (m, 2H, CH_2), 2.43 (t, 1H, CH), 2.50 (m, 1H, CH), 2.58 (m, 1H, 3α-CH), 3.16 (m, 1H, 5α-CH), 3.48 (d, 1H, CH), 4.05 (q, 4H, $2CH_2$), 4.22 (t, 1H, CH), 7.16-7.64 (m, 4H, Ar-H), 10.05 (s, 1H, OH, exchangeable with D_2O). MS (EI): m/z % = 618 [M^+, 8]. Anal. $C_{33}H_{45}BrO_6$ (617.61): Calcd C, 64.18; H, 7.34; Br, 12.94; found C, 64.11; H, 7.30; Br, 12.90.

16-[(α-Diethyl)malonyl)-4-methoxyphenyl]-3β-hydroxyl-androstan-17-one (9c).

Yield 52%, mp. 226-228°C, $[\alpha]_D^{25}$ = + 117 (c 1, $CHCl_3$); IR (KBr): 3654 (OH), 3090 (CH, Ar), 2962 (CH, Aliph), 1734 (C=O), 1610 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.85, 0.94 (2s, 6H, $2CH_3$), 0.98-1.14 (m, 1H, CH), 1.20-1.30 (m, 10H, $2CH_2$ + $2CH_3$), 1.36-1.85 (m, 10H, $5CH_2$), 1.96 (m, 1H, CH), 2.16-2.34 (m, 2H, CH_2), 2.42 (t, 1H, CH), 2.51 (m, 1H, CH), 2.58 (m, 1H, 3α-CH), 3.15 (m, 1H, 5α-CH), 3.33 (s, 3H, OCH_3), 3.50 (d, 1H, CH), 4.12 (q, 4H, $2CH_2$), 4.25 (t, 1H, CH), 7.06-7.58 (m, 4H, Ar-H), 10.12 (s, 1H, OH, exchangeable with D_2O). MS (EI): m/z % = 569 [M^+, 5]. Anal. $C_{34}H_{48}O_7$ (568.74): Calcd C, 71.80; H, 8.51; found C, 71.72; H, 8.45.

Synthesis of 16-[substituted phenyl]-methylene-5α-androstan-3β-ol 10a,b

A solution of **1c,d** (10 mmol) and catalytic amount of Adam's catalyst (25 mg) in absolute ethanol (20 ml) was shaken and heated at 80°C in hydrogen atmosphere at 5 bars for 5 h. The reaction mixture was filtered off, the obtained filtrate was evaporated under reduced pressure to dryness. The obtained residue was crystallized from ethanol to give derivatives **10a,b,** respectively.

16-[4-Chlorophenyl]-methylene-5α-androstan-3β-ol (10a).

Yield.90%, mp. 238-240°C, $[\alpha]_D^{25}$ = + 120 (c 1, $CHCl_3$); IR (KBr): 3560 (OH), 3050 (CH, Ar), 2950 (CH, Aliph), 1618 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.84, 0.95 (2s, 6H, $2CH_3$), 0.98-1.14 (m, 1H, CH), 1.18-1.87 (m, 14H, $7CH_2$), 1.95-2.00 (m, 3H, CH+CH_2), 2.25-2.36 (m, 2H, CH_2), 2.50 (m, 1H, CH), 2.58 (m, 1H, 3α-CH), 3.16 (m, 1H, 5α-CH), 6.72 (s, 1H, C=CH), 7.08-7.65 (m, 4H, Ar-H), 9.98 (s, 1H, OH, exchangeable with D_2O). MS (EI): m/z % = 399 [M^+, 16]. Anal. $C_{26}H_{35}ClO$ (399.01): Calcd C, 78.26; H, 8.84; Cl, 8.89; found C, 78.20; H, 8.80; Cl, 8.83.

16-[4-Methoxyphenyl]-methylene-5α-androstan-3β-ol (10b).

Yield.94%, mp. 221-223°C, $[\alpha]_D^{25}$ = + 123 (c 1, $CHCl_3$); IR (KBr): 3568 (OH), 3075 (CH, Ar), 2965 (CH, Aliph), 1615 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.86, 0.96 (2s, 6H, $2CH_3$), 1.02-1.15 (m, 1H, CH), 1.20-1.85 (m, 14H, $7CH_2$), 1.96-2.02 (m, 3H, CH+CH_2), 2.26-2.35 (m, 2H, CH_2), 2.48 (m, 1H, CH), 2.56 (m, 1H, 3α-CH), 3.14 (m, 1H, 5α-CH), 3.42 (s, 3H, OCH_3), 6.75 (s, 1H, C=CH), 7.05-7.60 (m, 4H, Ar-H), 9.96 (s, 1H, OH, exchangeable with D_2O). MS (EI): m/z % = 395 [M^+, 6]. Anal. $C_{27}H_{38}O_2$ (394.59): Calcd C, 82.18; H, 9.71; found C, 82.10; H, 9.66.

Synthesis of 16-[substituted phenyl]-methylene-5α-androstan-3-one 11a,b

A solution of **10a,b** (4 mmol) and killian solution (6 ml) [freshly prepared from potassium chromate (6 gm), sulfuric acid (8 ml), water (27 ml)] in glacial acetic acid (26 ml) was stirred at room temperature for 30 min. Excess of chromic acid was destroyed by addition of methanol, while warming filtered off, washed with water, dried and crystallized from methanol to give oxidized products **12a,b**, respectively.

16-[4-Chlorophenyl]-methylene-5α-androstan-3-one (11a).

Yield, 84%, mp. 179-181°C, $[\alpha]_D^{25}$ = + 168 (c 1, $CHCl_3$); IR (KBr): 3042 (CH, Ar), 2935 (CH, Aliph.), 1870 (C=O), 1622 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.83, 0.96 (2s, 6H, $2CH_3$), 0.99-1.15 (m, 1H, CH), 1.17-1.87 (m, 14H, $7CH_2$), 1.94-2.01 (m, 3H, CH+CH_2), 2.23-2.35 (m, 2H, CH_2), 2.50 (m, 1H, CH), 2.60 (m, 1H, 3α-CH), 6.68 (s, 1H, C=CH), 7.12-7.64 (m, 4H, Ar-H). MS (EI): m/z % = 397 [M^+, 10]. Anal. $C_{26}H_{33}ClO$ (396.99): Calcd C, 78.66; H, 8.38; Cl, 8.93; found C, 78.58; H, 8.32; Cl, 8.88.

16-[4-Methoxyphenyl]-methylene-5α-androstan-3β-one (11b).

Yield.68%, mp. 268-270°C, $[\alpha]_D^{25}$ = + 167 (c 1, $CHCl_3$); IR (KBr): 3082 (CH, Ar), 2956 (CH, Aliph), 1872 (C=O), 1612 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.86, 0.94 (2s, 6H, $2CH_3$), 0.98-1.14 (m, 1H, CH), 1.18-1.88 (m, 14H, $7CH_2$), 1.95-2.00 (m, 3H, CH+CH_2), 2.25-2.36 (m, 2H, CH_2), 2.46 (m, 1H, CH), 2.56 (m, 1H, 3α-CH), 3.38 (s, 3H, OCH_3), 6.70 (s, 1H, C=CH), 7.06-7.62 (m, 4H, Ar-H). MS (EI): m/z % = 392 [M^+, 12]. Anal. $C_{27}H_{36}O_2$ (392.57): Calcd C, 82.61; H, 9.24; found C, 82.55; H, 9.20.

Synthesis of 16-[substituted phenyl]-methylene-5α-androstan-3β-yl-acetate 12a,b

A solution of **10a,b** (4 mmol) in acetyl chloride (5 ml) was stand overnight at room temperature without stirring. The reaction mixture was evaporated under reduced pressure to dryness. The obtained residue was solidified with water, filtered off, washed with water, dried and crystallized from methyl acetate to give protected products **12a,b,** respectively.

16-[4-Chlorophenyl]-methylene-5α-androstan-3β-yl-acetate (12a).

Yield.82%, mp. 268-270°C, $[\alpha]_D^{25}$ = + 119 (c 1, $CHCl_3$); IR (KBr): 3038 (CH, Ar), 2964 (CH, Aliph), 1720 (C=O), 1620 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.85, 0.95 (2s, 6H, $2CH_3$), 0.98-1.12 (m, 1H, CH), 1.18-1.84 (m, 14H, $7CH_2$), 1.96-2.02 (m, 3H, CH+CH_2), 2.10 (s, 3H, $COCH_3$), 2.22-2.35 (m, 2H, CH_2), 2.51 (m, 1H, CH), 2.59 (m, 1H, 3α-CH), 3.14 (m, 1H, 5α-CH), 6.70 (s, 1H, C=CH), 7.06-7.66 (m, 4H, Ar-H). MS (EI): m/z % = 441 [M^+, 8]. Anal. $C_{28}H_{37}ClO_2$ (441.05): Calcd C, 76.25; H, 8.46; Cl, 8.04; found C, 76.20; H, 8.40; Cl, 8.00.

16-[4-Methoxyphenyl]-methylene-5α-androstan-3β-yl-acetate (12b).

Yield.90%, mp. 298-300°C, $[\alpha]_D^{25}$ = + 128 (c 1, $CHCl_3$); IR (KBr): 3064 (CH, Ar), 2954 (CH, Aliph), 1718 (C=O), 1616 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.86, 0.96 (2s, 6H, $2CH_3$), 1.02-1.15 (m, 1H, CH), 1.20-1.85 (m, 14H, $7CH_2$), 1.96-2.02 (m, 3H, CH+CH_2), 2.12 (s, 3H, $COCH_3$), 2.26-2.35 (m, 2H, CH_2), 2.48 (m, 1H, CH), 2.56 (m, 1H, 3α-CH), 3.14 (m, 1H, 5α-CH), 3.42 (s, 3H, OCH_3), 6.75 (s, 1H, C=CH), 7.05-7.60 (m, 4H, Ar-H). MS (EI): m/z % = 437 [M^+, 15]. Anal. $C_{29}H_{40}O_3$ (436.63): Calcd C, 79.77; H, 9.23; found C, 79.70; H, 9.17.

Synthesis of 16-[substituted phenyl]-methylene-5α-androstan-3β-yl-acetate 13a,b

A solution of **10a,b** (4 mmol) in trifluoroacetic anhydride (10 ml) was left aside overnight at room temperature without stirring. The reaction mixture was evaporated under reduced pressure to dryness. The obtained residue was solidified with aqueous sodium carbonate, filtered off, washed with water, dried and crystallized from ethanol to give protected products **13a,b,** respectively.

16-[4-Chlorophenyl]-methylene-5α-androstan-3β-yl-trifluoroacetate (13a).

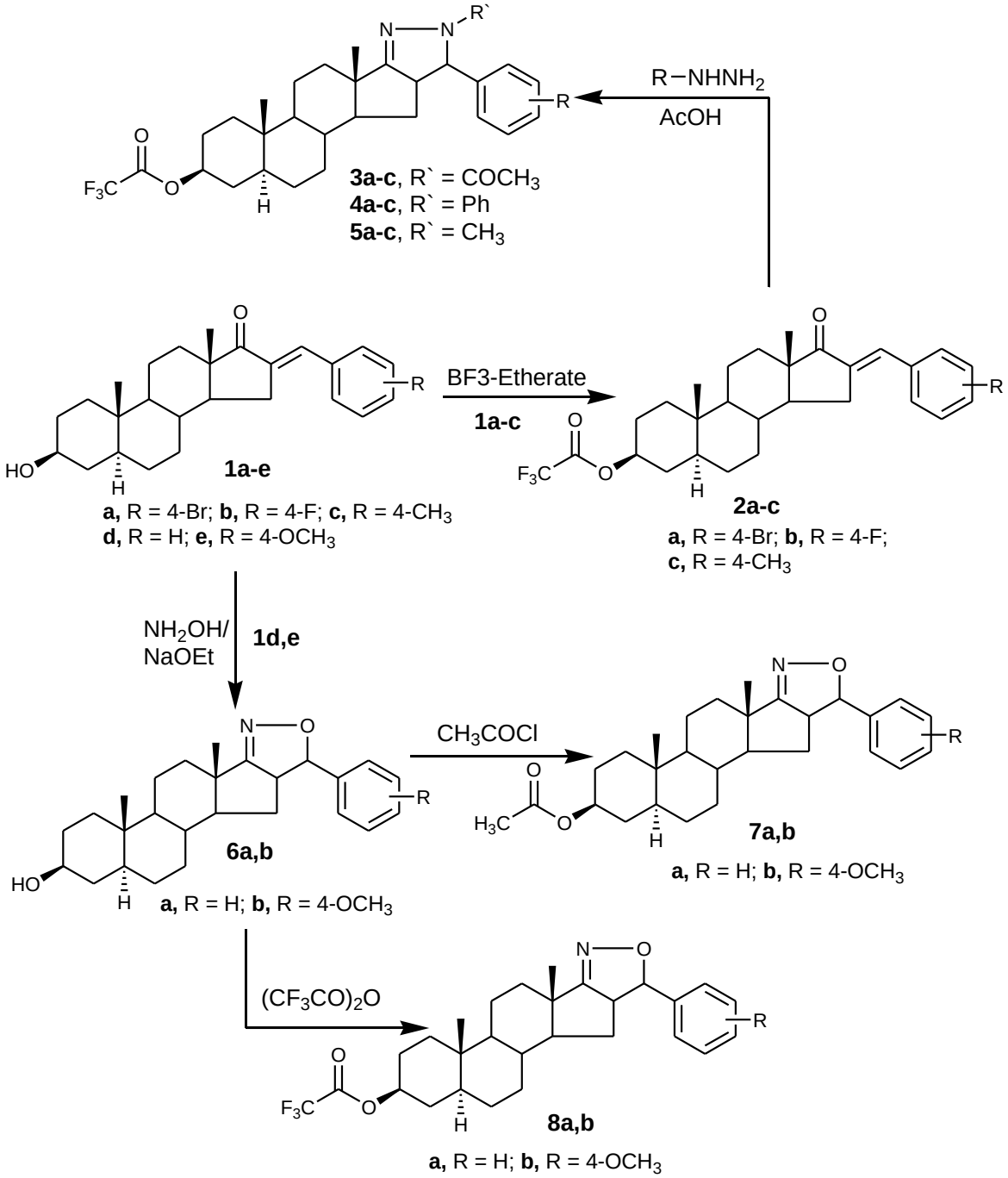
Yield.86%, mp. 275-277°C, $[\alpha]_D^{25}$ = + 127 (c 1, $CHCl_3$); IR (KBr): 3068 (CH, Ar), 2956 (CH, Aliph), 1721 (C=O), 1616 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.85, 0.95 (2s, 6H, $2CH_3$), 0.99-1.12 (m, 1H, CH), 1.18-1.89 (m, 14H, $7CH_2$), 1.95-2.01 (m, 3H, CH+CH_2), 2.20-2.36 (m, 2H, CH_2), 2.51 (m, 1H, CH), 2.58 (m, 1H, 3α-CH), 3.13 (m, 1H, 5α-CH), 6.68 (s, 1H, C=CH), 7.10-7.64 (m, 4H, Ar-H). MS (EI): m/z % = 495 [M^+, 22]. Anal. $C_{28}H_{34}ClF_3O_2$ (495.02): Calcd C, 67.94; H, 6.92; Cl, 7.16; found C, 67.86; H, 6.86; Cl, 7.10.

16-[4-Methoxyphenyl]-methylene-5α-androstan-3β-yl-trifluoroacetate (13b).

Yield.94%, mp. 258-360°C, $[\alpha]_D^{25}$ = + 136 (c 1, $CHCl_3$); IR (KBr): 3082 (CH, Ar), 2966 (CH, Aliph), 1722 (C=O), 1615 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.82, 0.95 (2s, 6H, $2CH_3$), 1.00-1.16 (m, 1H, CH), 1.20-1.84 (m, 14H, $7CH_2$), 1.95-2.00 (m, 3H, CH+CH_2), 2.26-2.34 (m, 2H, CH_2), 2.47 (m, 1H, CH), 2.54 (m, 1H, 3α-CH), 3.12 (m, 1H, 5α-CH), 3.40 (s, 3H, OCH_3), 6.70 (s, 1H, C=CH), 7.02-7.58 (m, 4H, Ar-H). MS (EI): m/z % = 490 [M^+, 5]. Anal. $C_{29}H_{37}F_3O_3$ (490.60): Calcd C, 71.00; H, 7.60; F, 11.62; found C, 70.92; H, 7.55.

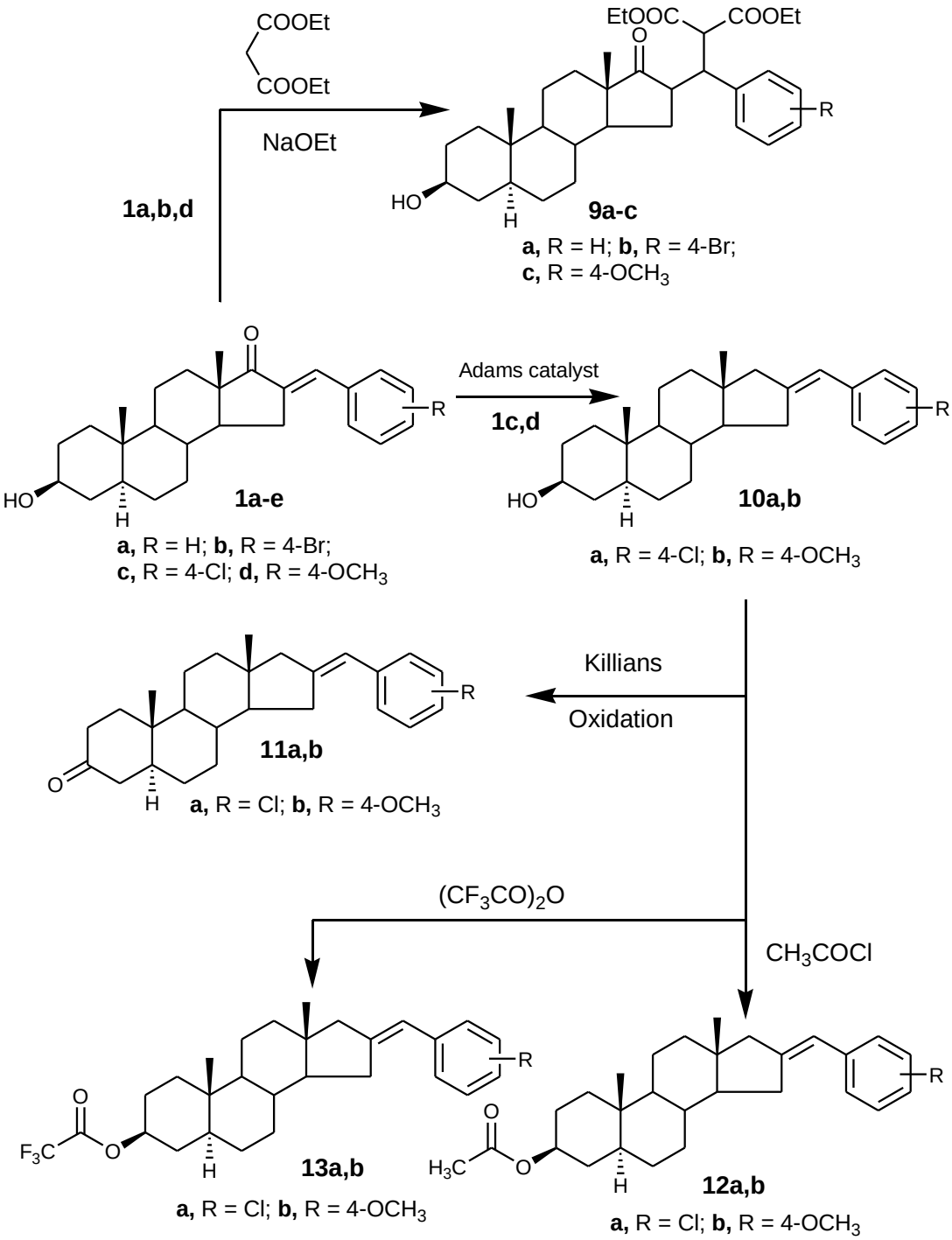
3. Results and Discussion

A series of substituted androstanopyrazoline and androstanoisoxazole and their derivatives **3-13**have been prepared by using arylidine derivatives **1a-e** and **2a-c** as starting materials. The reaction of protected arylmethylene of 3β-hydroxyandrostan-17-one derivatives **2a-c** with hydrazine derivatives, namely, acetic acid hydrazide, phenylhydrazine or methylhydrazine in glacial acetic acid to yield the corresponding androstano-N-substituted pyrazoline derivatives **3a-c, 4a-c** and**5a-c**, respectively. But, coupling of **1d,e** with hydroxylamine hydrochloride in the presence of sodium methoxide to give the corresponding isoxazole derivatives **6a,b,** which was protected with acetyl chloride or trifluoroacetic anhydride to give the corresponding protected products **7a,b** and **8a,b**, respectively (Scheme 1).



Scheme 1

Additionally, the reaction of **1a,b,d** with diethyl malonate in the presence of sodium ethoxide afforded the corresponding diester derivatives **9a-c**, respectively. Also, treatment of **1c,d** with catalytic amount of Adam's catalyst gave the corresponding decarbonylation derivatives **10a,b**, which was oxidized with potassium chromate in sulfuric acid to give the corresponding oxidized products **11a,b,** respectively. Finally, compounds **10a,b** was treated with acetyl chloride or trifluoroacetic anhydride to give the corresponding protected products **12a,b** and **13a,b**, respectively (Scheme 2).



Scheme 2

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Corresponding author

Abd El-Galil E. Amr[1,2]

1Pharmaceutical Chemistry Department, College of Pharmacy, King Saud University, Riyadh 11451, Saudi Arabia

[2]Applied Organic Chemistry Department, National Research Center, Dokki, Cairo, Egypt

aeamr1963@yahoo.com

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