Steroids 112 (2016) 20–35

Contents lists available at ScienceDirect

Steroids

journal homepage: www.elsevier.com/locate/steroids

Design and synthesis of four steroid-oxirane derivatives using some chemical tools

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ARTICLE INFO

Article history:
Received 8 October 2015
Received in revised form 13 April 2016
Accepted 29 April 2016
Available online 3 May 2016

Keywords:
Progesterone
Steroid derivatives
Chloroacetyl chloride
Oxirane ring

ABSTRACT

This study involved the synthesis of several new derivatives of progesterone, 11a-hydroxyprogesterone, 11a-*t*-butyldimethylsilanyloxyprogesterone, and andrenosterone. The new derivatives were prepared by condensation of the 4-en-3-one moiety of the four steroids with 2-hydroxy-1-naphthaldehyde to afford a series of 4-(*R*)-hydroxy-(2-hydroxynaphtalen-1-yl) adducts. These adducts were further modified by cyclization reactions of the dihydroxynaphthalenyl moieties with succinic acid, and the resulting cyclic succinates were then condensed with ethylenediamine to form imine derivatives at all available carbonyl groups. These compounds were then derivatized by *N*-acylation of the 11- and 17-imine nitrogens with chloroacetyl chloride and the resulting chloroacetamides were then condensed with 2-hydroxy-1-napthaldehyde in Darzens-type reactions forming the corresponding epoxy acetamides in the side chains. In addition, the chemical structure of steroid derivatives was confirmed by NMR spectroscopic data.

1. Introduction

Since several years ago the combinatory chemistry has been used to synthetize new steroid derivatives. In this sense, some rings have been bound to steroid nuclei for example, the direct connection of tetraaza[3.3.3.3]paracyclophane with bile acids to give steroid-cyclophane derivatives [1,2]. Another study, showed the reaction of tetraaza[6.1.6.1]paracyclophane with a bile acid analog to form a steroid-cyclophane derivative [3]. In addition, other type of steroid derivative such as drospirenone was prepared using the steroidal l7-espirolactone and lithium acetylide [4]. Another report [5] shows the synthesis of a thiazol-steroid derivative by the reaction of 6β-androstenedione with cyanothioacetamide. Additionally, a study indicated the preparation of a triazole-steroid derivative by the reaction of 3-methoxyestra-1,3,5(10)-trien-17α-azide with ethynylbenzene [6]. Another data showed the synthesis of a pregnenolone pyrazoline by reaction of the D-ring 16-ene-20-one moiety with phenylhydrazine [7]. Additionally, a steroid-pyranoxindole derivative was developed by reaction of the steroid-dicyanoalkene with a substituted isatin [8]. Another report [9] showed that dehydroepiandrosterone was condensed with 2-pyridine-carboxaldehyde to form the compound 19-(2′-pyridylmethylene)-17-oxo-5-androsten-3β-ol. All these experimental results show several procedures which are available for synthesis of several steroid derivatives; nevertheless, expensive reagents and special conditions are required. Therefore, the aim of this study involves the preparation of some steroid-oxirane derivatives from progesterone 11-hydroxy-progesterone, *tert*-butyl-dimethylsilanyloxy-progesterone and adrenosterone.

2. Results and discussion

In this study some oxirane-steroid derivatives were developed using progesterone, 11α-hydroxy-progesterone, 11α-tert-Buty-dimethylsilanyloxy-progesterone and adrenosterone as chemical tools (Scheme 1).

2.1. Protection oh hydroxyl group of 11α-hydroxyprogesterone

The first stage was accomplished by protecting of the hydroxyl group from 11α-hydroxy-progesterone (Scheme 2). It is important

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http://dx.doi.org/10.1016/j.steroids.2016.04.012
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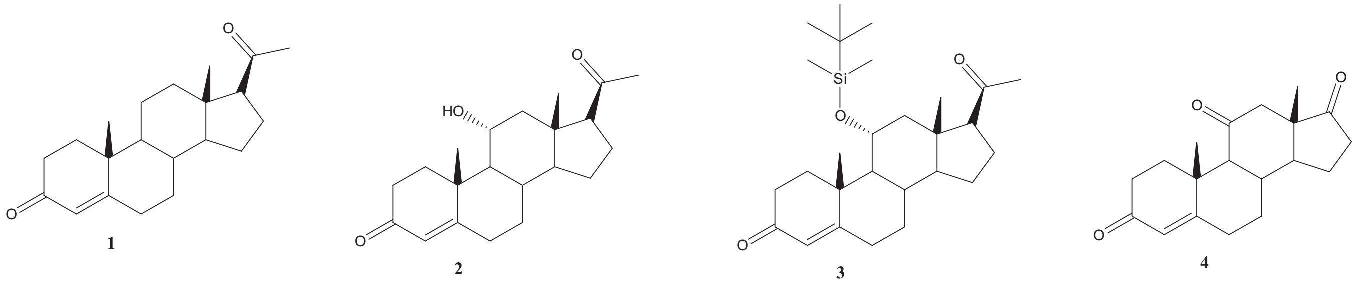
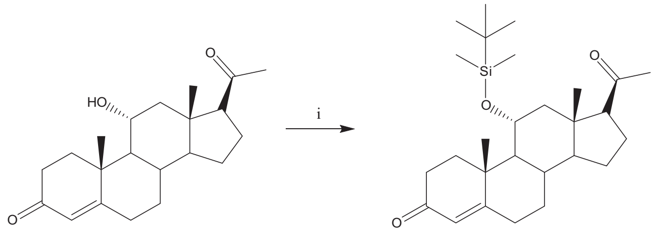


1 2 3 4

Scheme 1. Chemical structure of progesterone (**1**), 11α-hydroxy-progesterone (**2**), 11α-tert-Buty-dimethyl-silanyloxy-progesterone (**3**) and adrenosterone (**4**).



2 3

Scheme 2. Protection of hydroxyl group of 11α-hydroxy-progesterone (**2**) with *tert*-butyldimethylsilyl chloride to form 11α-*tert*-butydimethylsilanyloxy progesterone (**3**). i = $CHCl_3$/rt

to mention that several triorganosilyl groups have been employed for protection of hydroxyl groups such as tert-butyldimethylsilyl and tert-butyldiphenylsilyl [10,11]; in this study, 11α-hydroxy-progesterone was reacted with tert-butyldimethylsilyl chloride to form the compound **3**. It is noteworthy, that there is a report on the preparation of 11-silyl ether-progesterone derivative [12]; however the procedure used involves different conditions. Furthermore, the data shown do not indicate the melting point of the progesterone derivative. Therefore, in this study the melting point was reported at 143–145 °C. In addition, several signals involved on the ^{1}H NMR and ^{13}C NMR spectra were found; for example, the ^{1}H NMR spectrum of **3** showed signals at 0.08 and 0.90 ppm for methyl groups involved in the *tert*-butyldimethylsilane fragment; at 0.76 and 1.38 ppm for methyl groups bound to steroid nucleus; at 1.04–1.26, 1.40–1.98 and 2.18–5.60 ppm for steroid moiety; at 2.12 ppm for ketone group. The ^{13}C NMR spectrum showed several signals at −4.70, 18.00 and 25.80 ppm for methyl groups of *tert*-butyldimethylsilane fragment; at 14.88 and 19.60 ppm for methyl groups bound to steroid nucleus; at 31.20 ppm for methyl bound to ketone group; at 22.44–24.28 and 31.74–199.10 ppm for steroid moiety; at 208.48 ppm for ketone group. Finally, the presence of **3** was confirmed from GMS which showed a molecular ion at *m*/*z* 444.30.

2.2. Synthesis of allylic alcohols-steroids derivatives

It is important to mention that there are some protocols for preparation of allylic alcohols that involve reagents such as DMAP (4-Dimethylaminopyridine), $TiCl_4$/chalcogenide, Bu_3P/phenols, DABCO (1,4-diazabicyclo[2.2.2]octane), methoxide anion, $LiClO_4$ and tributylphosphine [13–17]; however, some these reagents are expensive and special conditions are required. Therefore, in this study some allylic alcohols (compounds **6**–**13**) were prepared using Bayliss-Hillman method [13–16]; by the reaction of compounds **1**–**4** with 2-hydroxy-1-naphthaldehyde in presence of imidazole. It is noteworthy, that the reaction involves the catalyst addition to the steroid. Furthermore, the nucleophile generated then adds to aldehyde. Finally, there is an elimination of the catalyst which leads to the allylic alcohols formation (Schemes 3 and 4). Furthermore, it is also important to mention that considering the possibility that the product could involve the formation of stereoisomers to provide the *R* and *S* epimers; the mixture of reaction was subjected to flash chromatography on silica gel with the methanol/hexane/ethyl acetate system to provide the enantiomers (*R*-*S*) and then NMR spectra were recorded. The ^{1}H NMR spectrum of compound 6 showed several signals at 0.68 and 1.12 ppm for methyl groups bound to steroid nucleus; at 6.40 ppm for methylene bound to ring A of steroid nucleus; at 7.18–7.86 ppm for phenyl groups; at 8.34 for hydroxyl groups. The ^{13}C NMR spectrum showed several signals at 13.16–18.66 ppm for methyl groups bound to steroid nucleus; at 29.94 ppm methyl group bound to ketone group; at 62.70 ppm for methylene group bound to ring A of steroid; at 119.80–130.86, 135.98–151.14 ppm for phenyl groups; at 206.70 ppm for ketone group. Finally, the presence of 6 was confirmed from GMS which showed a molecular ion at *m*/*z* 486.27.

Another data showed a ^{1}H NMR spectrum of compound **8** showed several signals at 0.80 and 1.16 ppm for methyl groups bound to steroid nucleus; at 2.14 ppm for methyl group bound to ketone group; at 6.40 ppm for methylene group bound to A-ring of steroid nucleus; at 5.92 ppm for hydroxyl groups; at 7.18–7.86 ppm for phenyl groups; at 8.34 ppm for hydroxyl group. The ^{13}C NMR spectrum showed several signals at 15.16–20.00 ppm for methyl groups bound to steroid nucleus; at 31.10 ppm for methyl group bound to ketone group; at 119.80–130.86 and 135.92–151.14 ppm for phenyl groups; at 208.36 ppm for ketone. Furthermore, the presence of **8** was confirmed from GMS which showed a molecular ion at *m*/*z* 502.27.

In addition, the ^{1}H NMR spectrum of compound **10** showed several signals at 0.88 and 0.90 ppm for methyl groups involved in the *tert*-butyldimethylsilane fragment; at 0.76 and 1.18 ppm for methyl groups bound to steroid nucleus; at 2.12 ppm for methyl group bound to ketone; at 6.40 ppm for methylene group bound to A ring of steroid nucleus; at 7.18–7.82 ppm for phenyl groups; at 8.32 ppm for hydroxyl groups. The ^{13}C NMR spectrum showed several signals at −4.70, 17.96 and 25.80 for methyl groups bound to steroid nucleus; at 14.88 and 20.00 ppm for methyl group bound to steroid nucleus; at 31.20 ppm for methyl group bound to ketone; at 62.70 ppm for carbon bound to A ring of steroid nucleus; at 119.80–130.86 and 135.92–151.14 ppm for phenyl groups; at 208.48 ppm for ketone group. In addition, the presence of **10** was confirmed from GMS which showed a molecular ion at *m*/*z* 616.35.

Finally, the ^{1}H NMR spectrum of compound **12** showed several signals at 0.88 and 1.20 ppm for methyl groups bound to steroid nucleus; at 6.40 ppm for methylene group bound to A ring of steroid nucleus; at 7.18–7.84 ppm for phenyl groups; at 8.34 ppm for hydroxyl groups. The ^{13}C NMR spectrum showed several signals at 14.70 and 19.70 ppm for methyl groups bound to A-ring of steroid nucleus; at 62.76 ppm for carbon bound to hydroxyl group;