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# Chemoselective construction of novel steroid derivatives

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**Abstract**

α-Halo-α-heteroarylalkyllithiums, generated by deprotonation of the corresponding halides, when added promptly to steroids with C=O or C=NR groups, lead to epoxides and aziridines. The reactions are regio- and stereoselective; in fact, in the presence of more than one C=O group, the oxido or aziridino functions are formed uniquely at the C=O of C-17 (or C-20 depending on its position in the starting molecule), and the C-20(*R*) stereoisomer is often the only product isolated. Protection of the hydroxyl group present on several considered steroids was required, and it was accomplished through derivatization in acetyl, ether, or lactone. 

*Keywords:* α-Halo-α-heteroarylalkyllithiums; Steroids; Oxiranes; Aziridines; Lactones

## 1. Introduction

Steroids represent an extensive and important class of biologically active compounds that are widely used in the pharmacological industry [1]. Many functional and structural modifications of steroids have been recently investigated in order to extend the already broad range of biological activity shown by these compounds and to increase their selectivity [2]. We hypothesized that the introduction of an oxido or aziridino function could play a key role in improving the biological activity of steroids and consequently, in the development of new, pharmacologically active compounds [3–6].

Interest towards this kind of steroid modification is due to the intense strain present in compounds, such as oxiranes and aziridines [7–9]. The ring strain makes them easy to open and suitable for further reactions and then, further modifications. Oxido and aziridino functions are actually known to be useful intermediates in the preparation of a great variety of bioorganic molecules, such as aminoacids [10], aminosugars [11], and antibiotics [12]. Moreover, in the biological environment, they may efficiently bind the nucleophilic sites of several biomolecules, particularly in DNA [13]. We have recently found that α-halo-α-heteroarylalkyllithiums, easily produced by deprotonation of the corresponding halides, lead to the formation of epoxides [14] and aziridines [15] if added to a solution of carbonylic compounds and imines (Scheme 1).

Since many natural steroids contain one or more carbonylic functions, we investigated the possibility of transforming these compounds with completely analogous reactions in oxiranyl and aziridinyl derivatives. The only example present in the literature is the synthesis of 17,20-epoxy-17-picolyl derived from the 5-α-androstene through oxidation of the corresponding 17-picolidene with the complex Cr(VI) oxidepyridine prepared in situ [16]. This procedure leads to modest yields (<40%) without any stereoselectivity. On the contrary, the method presented here seems very promising from the point of view of stereoselectivity and gives more satisfactory yields.

## 2. Experimental section

### 2.1. Characterization of steroids

$^1$H NMR spectra were recorded on Varian EM 360, EM 390, Varian XL-200, and Bruker AM 300 WB spectrometers; chemical shifts were recorded in parts per million ($\delta$) from the internal standard using $CDCl_3$ as solvent. IR spectra were recorded on a Perkin-Elmer spectrometer Model 598. GC analyses were carried out with a Hewlett-Packard MP-5890 series II gas chromatograph (dimethylsilicon capillary column, 30 m, 0.25 mm i.d.) only for compounds for which MS analyses are reported. GC–MS spectrometry analyses were performed on a HP-5890 series II gas chromatograph equipped with HP-5971 mass selective detector operating at 70 eV (E.I.). Melting points are uncorrected.

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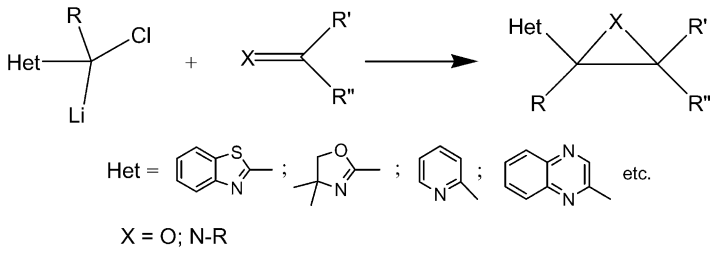



Scheme 1. Synthesis of oxiranes and aziridines through a Darzens-type reaction [8,9].

Flash chromatography was performed with Merck 230–400 mesh silica gel. All reactions were conducted in oven-dried glassware under a nitrogen atmosphere. Microanalyses were performed on a Carlo Erba C, H, N analyzer.

### 2.2. Materials

Commercial grade tetrahydrofuran (THF) was purified by distillation (twice) from sodium wire under a nitrogen atmosphere. Petroleum ether refers to the 40–70 °C boiling fraction. 2-Chloromethyl-pyridine, 3-chloromethyl-pyridine, and 2-chloromethyl-quinoline were obtained from their respective hydrochlorides (Aldrich) by treatment with a 10% NaOH solution. 2-Chloromethyl-benzothiazole, 2-(1-chloroethyl)-benzothiazole [14], 2-chloromethyl-4,4-dimethyl-2-oxazoline [17], and 2-(1-chloroethyl)-4,4-dimethyl-2-oxazoline [18] were prepared as reported.

All steroids and all other chemicals were of commercial grade (Aldrich–Fluka) and used without further purification or eventually crystallized prior to the use. Acetyl-steroids (**2a**, **e**, **f**) were obtained as follows: a solution of steroid (1.0 g) (estrone or *trans*-androsterone or *cis*-androsterone) and sodium acetate (1.0 g) in acetic anhydride (10.0 ml) was warmed at 70–80 °C for 1 h. Water (100 ml) was added, and the precipitate of the acetyl-steroid was isolated by filtration, yield 95%.

3-Allyloxy-estrone (**2b**) was obtained by the reaction of the estrone (1.0 g, 3.7 mmol) in acetone (20 ml) with allyl-bromide (1.0 g) and NaOH (0.4 g, 1.0 mmol). The mixture was warmed at 60 °C for 1 h, and after a TLC check (eluent: petroleum ether/ether 1/1), water (150 ml) was added. The precipitate obtained was filtered, dried, and analyzed as *3-allyloxy-estrone* (**2b**), yield 98%; m.p. = 105−106 °C (from petroleum ether 40–70 °C); $^1$H NMR ($CDCl_3$) $\delta$: 0.91–2.90 (m, 18H), 4.50 (t, 1H, $J$ = 1.4 Hz), 4.53 (t, 1H, $J$ = 1.4 Hz), 5.28 (dd, 1H, $J$ = 10, 1.4 Hz), 5.40 (dd, 1H, $J$ = 16, 1.4 Hz), 5.96–6.13 (m, 1H), 6.60–7.3 (m, 3H); MS *m/e* (rel. int.): 310 (100, $M^+$), 225 (42), 212 (23), 186 (38); IR ($CHCl_3$) cm$^{-1}$: 3065, 3020, 2920, 2850, 1735, 1605, 1250, 1230. El. An. Calcd. for $C_{21}H_{26}O_2$: C, 81.29; H, 8.38. Found: C, 81.01; H, 8.44.

Lactones (**2c**, **d**) were obtained by intermolecular cyclocarbonylation of a mixture of 2-allylestrone and 4-allylestrone after a Claisen rearrangement of 3-allyloxy-estrone (**2b**). Procedure: (**2b**) (980 mg) was dissolved in *N*,*N*-diethylaniline (10 ml) and heated to 220 °C. After 2 h, the TLC control showed completion of the reaction. Then, the mixture was cooled to room temperature, and ether was added (100 ml). Aniline was removed by washing with 10% HCl three times (caution, exothermic reaction). Evaporation of the ether and drying over $Na_2SO_4$ under reduced pressure left a residue: 87% of a mixture of 2-allylestrone, and 4-allylestrone, ratio 1:2 (via GC–MS). This residue was dissolved with 0.01 mmol of $Pd(OAc)_2$ and 0.04 mmol of [1-4-bis(diphenylphosphino)butane] (dppb) in 5 ml of toluene and placed in a 45 ml autoclave. The autoclave was purged, pressurized (600 psi of CO + $H_2$), and heated to 110–120 °C. After 24 h, the reaction was cooled to room temperature, filtered through celite, and concentrated by rotary evaporation. Separation and purification of the lactones (**2c**, **d**) (ratio 2:1) were achieved by silica gel column chromatography (eluent: petroleum ether/ether 1/1). *4-(3′-Carboxypropyl)estrone lactone* (**2c**): m.p. = 67−70 °C (from petroleum ether 40–70 °C); $^1$H NMR ($CDCl_3$) $\delta$: 0.9–2.83 (m, 24 H), 6.90 (d, 1H, $J$ = 8.5 Hz), 7.2 (d, 1H, $J$ = 8.5 Hz); MS *m/e* (rel. int.): 338 (100, $M^+$), 320 (8), 293 (15), 238 (90); IR ($CHCl_3$) cm$^{-1}$: 3030, 2925, 2850, 1755, 1735, 1125. El. An. Calcd. for $C_{22}H_{26}O_3$: C, 78.10; H, 7.78. Found: C, 78.03; H, 7.92. *2-(3′-Carboxypropyl)estrone lactone* (**2d**): m.p. = 207−209 °C (from petroleum ether 40–70 °C); $^1$H NMR ($CDCl_3$) $\delta$: 0.91–2.91 (m, 24 H), 6.80 (s, 1H), 7.08 (s, 1H); MS *m/e* (rel. int.): 338 (56, $M^+$), 310 (2), 283 (100); IR ($CHCl_3$) cm$^{-1}$: 3030, 2920, 2850, 1755, 1735, 1120. El. An. Calcd. for $C_{22}H_{26}O_3$: C, 78.10; H, 7.78. Found: C, 77.79; H, 8.02.

Imine (**2h**) was synthesized from 3-allyloxy-estrone (**2b**) with a modified Westeimer [19] method. An aniline solution (1.0 mmol) and 3-allyloxy-estrone (0.5 mmol) in dry ether (30 ml) were added to 10 g of Sieves (5 Å). The mixture was preserved under a nitrogen atmosphere overnight; then, ether (20 ml) was added, and the sieves were renewed. After 5 h, the mixture was filtered and chromatographed by silica gel column (eluent: petroleum ether/ether 1/1). Unreacted 3-allyloxy-estrone (**2b**) was recovered (0.2 mmol) and imine (**2h**) was isolated, yield 98%; m.p. = 132−134 °C (from $CH_2Cl_2$-EtOAc); $^1$H NMR ($CDCl_3$) $\delta$: 1.02 (s, 3H), 1.5–2.5 (m, 13H), 2.85–2.95 (m, 2H), 4.48–4.54 (m, 2H), 5.24–5.45 (m, 2H), 5.96–6.13 (m, 1H), 6.66–7.32 (m, 8H). $^{13}$C NMR ($CDCl_3$) $\delta$: 16, 23, 26, 27, 28, 30, 34, 38, 44, 46, 52, 69, 112, 115, 117, 119, 123, 126, 129, 132, 135, 138, 152, 156;

MS *m/e* (rel. int.): 385 (60, $M^+$), 185 (23), 172 (100); IR ($CHCl_3$) $cm^{-1}$: 3060, 3020, 2930, 2860, 1670, 1600, 1500, 1230.

### 2.3. Representative experimental procedure for the coupling reaction

The reaction of 2-benzothiazolylchloromethyllithium (**1a**) with 3-allyloxy-estrone (**2b**) is described as an example. An amount of 1 ml of a 2.4 M hexane solution of *n*-butyllithium (*n*-BuLi) was added to di-*iso*propylamine (2.4 mmol) in 10 ml of THF at 0 °C. The resulting yellow solution was cooled to −78 °C, and solutions of (**2b**) (0.620 g, 2.0 mmol) and of (**1a**) (0.372 g, 2.0 mmol) in 5 ml of THF were added dropwise. After 1 h at −78 °C, the reaction mixture was allowed to warm to room temperature and quenched with aqueous $NH_4Cl$ after 3 h. Extraction with ether (3 × 25 ml), drying over $Na_2SO_4$, and evaporation of the solvent under reduced pressure left a residue that was column chromatographed (silica gel, petroleum ether/ether 7/3 as eluent) to give the following epoxides [C-20(*R*)/C-20(*S*): 40/33]. All the other coupling reactions were carried out in the same manner, and the ratios are reported in Table 1.

#### 2.3.1. 17β,20(R)-Epoxy-20-(2-benzothyazolyl)-3-allyloxy-estrone (**3*a***)

Melting point = 159−161 °C (from ether–petroleum ether 40–70 °C); $^1H$ NMR ($CDCl_3$) $\delta$: 0.85–2.9 (m, 18H), 4.30 (s, 1H), 4.45–4.55 (m, 2H); 5.2–5.45 (m, 2H), 5.95–6.15 (m, 1H), 6.6–8.1 (m, 7H); IR ($CHCl_3$) $cm^{-1}$: 3060, 3020, 2920, 2880, 1600, 1490, 1230. El. An. Calcd. for $C_{29}H_{31}NO_2S$: C, 76.15; H, 6.78; N, 3.06; S, 7.00. Found: C, 75.90; H, 6.90; N, 2.91; S, 7.20.

Table 1
Reaction of α-halo-α-heteroarylalkyllithiums **1a**–**g** with steroids **2a**–**h** in THF at −78 °C under nitrogen (**1a**–**g**) + (**2a**–**h**) → (**3a**–**q**)

| Entry | Coupling reaction | Product | Yield (%) | C-20(*R*)/C-20(*S*) ratio |
|---|---|---|---|---|
| 1 | **1a** + **2b** | **3a** | 73 | 40/33 |
| 2 | **1e** + **2b** | **3b** | 52 | 100/0 |
| 3 | **1e** + **2a** | **3c** | 40 | 15/25 |
| 4 | **1e** + **2f** | **3d** | 50 | 20/30 |
| 5 | **1b** + **2f** | **3e** | 98 | 42/56 |
| 6 | **1c** + **2e** | **3f** | 45 | 20/30 |
| 7 | **1a** + **2e** | **3g** | 70 | 55/15 |
| 8 | **1a** + **2c** | **3h** | 50 | 100/0 |
| 9 | **1f** + **2c** | **3I** | 65 | 100/0 |
| 10 | **1f** + **2d** | **3j** | 75 | 100/0 |
| 11 | **1g** + **2c** | **3k** | 68 | 100/0 |
| 12 | **1g** + **2d** | **3l** | 60 | 100/0 |
| 13 | **1a** + **2g** | **3m** | 64 | 100/0[a] |
| 14 | **1b** + **2g** | **3n** | 60 | 100/0[a] |
| 15 | **1d** + **2g** | **3o** | 55 | 100/0[a] |
| 16 | **1a** + **2h** | **3p** | 52 | 100/0 |
| 17 | **1e** + **2h** | **3q** | 48 | 100/0 |

[a] 100 is referred to the C-20(*S*), C-21(*R*) diastereoisomer, the unique stereoisomer isolated among the four possible.

*17β,20(S)-Epoxy-20-(2-benzothyazolyl)-3-allyloxy-estrone*: m.p. = 164−166 °C (from ether–petroleum ether 40–70 °C); $^1H$ NMR ($CDCl_3$) $\delta$: 0.85–2.9 (m, 18H), 4.4–4.7 (m, 3H), 5.2–5.5 (m, 2H), 5.95–6.15 (m, 1H), 6.6–8.1 (m, 7H); IR ($CHCl_3$) $cm^{-1}$: 3060, 3020, 2920, 2880, 1600, 1490, 1230. El. Anal. Calcd. for $C_{29}H_{31}NO_2S$: C, 76.15; H, 6.78; N, 3.06; S, 7.00. Found: C, 75.98; H, 6.95; N, 2.95; S, 7.12.

#### 2.3.2. 17β,20(R)-Epoxy-20-(2-quinolinyl)-3-allyloxy-estrone (**3*b***)

Melting point = 43−45 °C (from ether–petroleum ether 40–70 °C); $^1H$ NMR ($CDCl_3$.) $\delta$: 0.85–2.8 (m, 18H), 4.50 (s, 1H), 4.52–4.56 (m, 2H), 5.20–5.45 (m, 2H), 5.95–6.15 (m, 1H), 6.6–8.3 (m, 9H); IR ($CHCl_3$) $cm^{-1}$: 3060, 3020, 2930, 2860, 1720, 1600, 1440, 1375, 1160. El. An. Calcd. for $C_{31}H_{33}NO_2$: C, 82.45; H, 7.36; N, 3.10: Found: C, 81.61; H, 7.70; N, 2.95.

#### 2.3.3. 17β,20(R)-Epoxy-20-(2-quinolinyl)-3-acetoxy-estrone (**3*c***)

Melting point = 62−65 °C (from ether–petroleum ether 40–70 °C); $^1H$ NMR ($CDCl_3$) $\delta$: 0.85–2.8 (m, 21H), 4.85 (s, 1H), 6.7–8.35 (m, 9H): IR ($CHCl_3$) $cm^{-1}$: 3060, 3020, 2930, 2860, 1720, 1600, 1440, 1375, 1160. El. An. Calcd. for $C_{30}H_{31}NO_3$: C, 79.44; H, 6.89; N, 3.08. Found: C, 78.52; H, 6.95; N, 2.95. *17β,20(S)-Epoxy-20-(2-quinolinyl)-3-acetoxy-estrone*: m.p. = 85−87 °C (from ether–petroleum ether 40–70 °C); $^1H$ NMR ($CDCl_3$) $\delta$: 0.85–2.8 (m, 21H), 4.65 (s, 1H), 6.7–8.35 (m, 9H); IR ($CHCl_3$) $cm^{-1}$: 3060, 3020, 2930, 2860, 1720, 1600, 1440, 1375, 1160. El. An. Calcd. for $C_{30}H_{31}NO_3$: C, 79.44; H, 6.89; N, 3.08. Found: C, 78.72; H, 6.97; N, 3.05.

#### 2.3.4. 17β-20(R)-Epoxy-20-(2-quinolinyl)-3β-acetoxy-5α-androstan (**3*d***)

Melting point = 162−165 °C (from ether–petroleum ether 40–70 °C); $^1H$ NMR ($CDCl_3$) $\delta$: 0.7–2.05 (m, 28H), 4.3 (s, 1H), 5 (s, 1H broad), 7.3–8.25 (m, 6H); IR ($CHCl_3$) $cm^{-1}$: 3020, 2930, 2860, 1730, 1440, 1375, 1260, 1160, 1010. El. An. Calcd. for $C_{31}H_{39}NO_3$: C, 78.61; H, 8.30; N, 2.96. Found: C, 77.91; H, 8.35; N, 2.85. *17β-20(S)-Epoxy-20-(2-quinolinyl)-3β-acetoxy-5α-androstan*: m.p. = 85−88 °C (from ether–petroleum ether 40–70 °C); $^1H$ NMR ($CDCl_3$) $\delta$: 0.75–2.1 (m, 28H), 4.45 (s, 1H), 5.1 (s, 1H broad), 7.3–8.25 (m, 6H); IR ($CHCl_3$) $cm^{-1}$: 3020, 2930, 2860, 1730, 1440, 1375, 1260, 1160, 1010. El. An. Calcd. for $C_{31}H_{39}NO_3$: C, 78.61; H, 8.30; N, 2.96. Found: C, 77.95; H, 8.25; N, 2.95.

#### 2.3.5. 17β-20(R)-Epoxy-20-methyl-20-(2-benzothyazolyl)-3β-acetoxy-5α-androstan (**3*e***)

Melting point = 45−47 °C (from petroleum ether 40–70 °C); $^1H$ NMR ($CDCl_3$) δ: 0.7–2.5 (m, 34H), 5.1 (s, 1H broad), 7.3–8.2 (m, 4H); IR ($CHCl_3$) $cm^{-1}$: 3020, 2935, 2860, 1730, 1435, 1375, 1260, 1160, 1010. El. An. Calcd. for $C_{28}H_{29}NO_3S$: C, 73.17; H, 6.36; N, 3.05; S,

6.98. Found: C, 71.76; H, 6.80; N, 2.80; S, 6.75. *17β-20(S)-Epoxy-20-methyl-20-(2-benzothyazolyl)-3β-acetoxy-5α-androstan*: m.p. = 197−199 °C (from petroleum ether 40–70 °C); $^1$H NMR ($CDCl_3$) δ: 0.7–2.2 (m, 34H), 5.1 (s, 1H broad), 7.35–8.2 (m, 4H); IR ($CHCl_3$) $cm^{-1}$: 3020, 2935, 2860, 1730, 1435, 1375, 1260, 1160, 1010. El. An. Calcd. for $C_{30}H_{39}NO_3S$: C, 73.17; H, 7.90; N, 2.81; S, 6.51. Found: C, 73.44; H, 7.20; N, 3.03; S, 6.65.

*2.3.6. 17β,20(R)-Epoxy-20-(2-pyridinyl)-3α-acetoxy-5α-androstan (**3f**)*

Oil; $^1$H NMR ($CDCl_3$) δ: 0.8–2.6 (m, 31H), 4.75 (s, 1H broad), 5.32 (s, lH), 7.25–8.8 (m, 4H); IR (film) $cm^{-1}$: 3020, 2930, 2850, 1725, 1450, 1375, 1255, 1150, 1010. El. An. Calcd. for $C_{27}H_{37}NO_3$: C, 76.56; H, 8.80; N, 3.30. Found: C, 75.10; H, 8.85; N, 2.95. *17β,20(S)-Epoxy-20-(2-pyridinyl)-3α-acetoxy-5α-androstan*: oil; $^1$H NMR ($CDCl_3$) δ: 0.8–2.4 (m, 31H), 4.8 (s, 1H broad), 5.55 (s, 1H), 7.1–8.8 (m, 4H); IR (film) $cm^{-1}$: 3020, 2930, 2850, 1725, 1450, 1370, 1260, 1150, 1010. El. An. Calcd. for $C_{27}H_{37}NO_3$: C, 76.56; H, 8.80; N, 3.30. Found: C, 75.30; H, 8.75; N, 2.90.

*2.3.7. 17β,20(R)-Epoxy-20-(2-benzothyazolyl)-3α-acetoxy-5α-androstan (**3g**)*

Melting point = 65−66 °C (from petroleum ether 40–70 °C); $^1$H NMR ($CDCl_3$) δ: 0.7–2.1 (m, 31H), 4.6 (s, 1H), 4.75 (s, 1H broad), 7.35–8.3 (m, 4H); IR ($CHCl_3$) $cm^{-1}$: 3060, 3020, 2930, 2850, 1725, 1440, 1375, 1260, 1020. El. An. Calcd. for $C_{29}H_{37}NO_3S$: C, 72.61; H, 7.78; N, 2.92; S, 6.68. Found: C, 71.90; H, 7.95; N, 2.75; S, 6.81. *17β,20(S)-Epoxy-20-(2-benzothyazolyl)-3α-acetoxy-5α-androstan*: m.p. = 82−83 °C (from petroleum ether 40–70 °C); $^1$H NMR ($CDCl_3$) δ: 0.7–2.03 (m, 31H), 4.38 (s, 1H), 4.75 (s, 1H broad), 7.4–8.3 (m, 4H); IR ($CHCl_3$) $cm^{-1}$: 3060, 3020, 2925, 2850, 1725, 1450, 1375, 1260, 1015. El. An. Calcd. for $C_{29}H_{37}NO_3S$: C, 72.61; H, 7.78; N, 2.92; S, 6.68. Found: C, 71.95; H, 7.75; N, 2.78; S, 6.83.

*2.3.8. 4-(3′-Carboxypropyl)-17β, 20(R)-epoxy-20-(2-benzothyazolyl)estrone lactone (**3h**)*

Melting point = 220−223 °C (from *n*-hexane); $^1$H NMR ($CDCl_3$) δ: 0.9–2.86 (m, 24H), 4.3 (s, 1H), 6.80 (d, 1H, $J$ = 8.5 Hz), 7.1 (d, 1H, $J$ = 8.5 Hz), 7.50–8.10 (m, 4H); IR ($CHCl_3$) $cm^{-1}$: 3050, 3020, 2900, 2840, 1735, 1410, 1250. El. An. Calcd. for $C_{30}H_{31}NO_3S$: C, 74.22; H, 6.39; N, 2.88; S, 6.59. Found: C, 74.08; H, 6.68; N, 3.10; S, 6.81.

*2.3.9. 4-(3′-Carboxypropyl)-17β,20(R)-epoxy-20-[(4,4-dimethyl)-2-oxazolyl]estrone lactone (**3i**)*

Melting point = 207−211 °C (with dec.), (from petroleum ether 40–70 °C); $^1$H NMR ($CDCl_3$) δ: 0.9–3.0 (m, 30H), 3.61 (s, 1H), 3.99 (s, 1H), 4.24 (s, 1H), 6.78 (d, 1H, $J$ = 8.5 Hz), 7.8 (d, 1H, $J$ = 8.5 Hz); IR ($CHCl_3$) $cm^{-1}$: 3030, 2910, 2850, 1730, 1610, 1500, 1250. El. An. Calcd. for $C_{28}H_{35}NO_4$: C, 74.80; H, 7.85; N, 3.10. Found: C, 74.52; H, 7.60; N, 3.05.

*2.3.10. 2-(3′-Carboxypropyl)-17β,20(R)-epoxy-20-[(4,4-dimethyl)-2-oxazolyl]estrone lactone (**3j**)*

Melting point = 166−170 °C (with dec.) (from *n*-hexane); $^1$H NMR ($CDCl_3$) δ: 0.9–2.95 (m, 30H), 3.59 (s, 1H), 4.03 (s, 1H), 4.27 (s, 1H), 6.67 (s, 1H), 7.0 (s, 1H); IR ($CDCl_3$) $cm^{-1}$: 3030, 2910, 2850, 1730, 1610, 1500, 1250. El. An. Calcd. for $C_{28}H_{35}NO_4$: C, 74.80; H, 7.85; N, 3.10. Found: C, 74.32; H, 7.68; N, 3.09.

*2.3.11. 4-(3′-Carboxypropyl)-17β,20(R)-epoxy-20-methyl-20-[(4,4-dimethyl)-2-oxazolyl]estrone lactone (**3k**)*

Melting point = 205−209 °C (from *n*-hexane); $^1$H NMR ($CDCl_3$) δ: 0.9–3.0 (m, 33H), 3.78–3.82 (m, 2H), 6.7 (d, 1H, $J$ = 8.5 Hz), 7.1 (d, 1H, $J$ = 8.5 Hz); IR ($CHCl_3$) $cm^{-1}$: 3060, 2960, 2850, 1750, 1660, 1600, 1450, 1230. El. An. Calcd. for $C_{29}H_{37}NO_4$: C, 75.13; H, 8.04; N, 3.02. Found: C, 74.80; H, 8.15; N, 3.10.

*2.3.12. 2-(3′-Carboxypropyl)-17β,20(R)-epoxy-20-methyl-20-[(4,4-dimethyl)-2-oxazolyl]estrone lactone (**3l**)*

Melting point = 160−165 °C (from petroleum ether 40–70 °C); $^1$H NMR ($CDCl_3$) δ: 0.9–3.0 (m, 33H), 3.78–3.82 (m, 2H), 6.8 (s, 1H), 7.1 (s, 1H); IR ($CHCl_3$) $cm^{-1}$: 3060, 3020, 2960, 2850, 1750, 1660, 1600, 1520, 1450, 1230. El. An. Calcd. for $C_{29}H_{37}NO_4$: C, 75.13; H, 8.04; N, 3.02. Found: C, 75.50; H, 8.25; N, 2.95.

*2.3.13. 20(S),21(R)-Epoxy-20-methyl-21-(2-benzothyazolyl)-androst-4-en-3-one (**3m**)*

Melting point = 233−234 °C (from petroleum ether 40–70 °C); $^1$H NMR ($CDCl_3$) δ: 0.7–2.6 (m, 29H), 4.2 (s, 1H), 5.87 (s, 1H), 7.5–8.3 (m, 4H); IR ($CHCl_3$) $cm^{-1}$: 3020, 2980, 2940, 2880, 1660, 1520, 1435, 1380, 1105. El. An. Calcd. for $C_{29}H_{35}NO_2S$: C, 75.45; H, 7.64; N, 3.03; S, 6.94. Found: C, 75.05; H, 7.72; N, 2.92; S, 7.01.

*2.3.14. 20(S),21(R)-Epoxy-20,21-dimethyl-21-(2-benzothyazolyl)-androst-4-en-3-one (**3n**)*

Melting point = 240−241 °C (with dec.) (from petroleum ether 40–70 °C); $^1$H NMR ($CDCl_3$) δ: 0.8–2.25 (m, 32H), 5.75 (s, 1H), 7.4–8.2 (m, 4H); IR ($CHCl_3$) $cm^{-1}$: 3020, 2975, 2935, 2880, 1660, 1520, 1435, 1380, 1100. El. An. Calcd. for $C_{30}H_{37}NO_2S$: C, 75.75; H, 7.84; N, 2.94; S, 6.74. Found: C, 75.30; H, 7.89; N, 2.94; S, 6.58.

*2.3.15. 20(S),21(R)-Epoxy-20-methyl-21-(3-pyridinyl)-androst-4-en-3-one (**3o**)*

Oil; $^1$H NMR ($CDCl_3$) δ: 0.7–2.6 (m, 29H), 4.65 (s, 1H), 5.8 (s, 1H), 7.3–8.75 (m, 4H); IR (film) $cm^{-1}$: 3020, 2970, 2875, 1660, 1450, 1375, 1355, 1230, 1110. El. An. Calcd. for $C_{27}H_{35}NO_2$: C, 79.96; H, 8.70; N, 3.45. Found: C, 79.58; H, 8.20; N, 3.25.

*2.3.16. 17β,20(R)-(N-Phenyl-aziridine)-20-(2-benzothiazolyl)-3-allyloxy-estrone (**3p**)*

Melting point = 137−139 °C (from ether–petroleum ether 40–70 °C); $^1$H NMR ($CDCl_3$) δ: 1.37–2.57 (m, 16H), 2.86–2.90 (m, 2H), 3.65 (s, 1H), 4.48–4.53 (m, 2H), 5.25–5.45 (m, 2H), 5.95–6.12 (m, 1H), 6.65–6.76 (m, 4H), 7.17–7.50 (m, 6H), 7.70–8.06 (m, 2H); IR ($CHCl_3$) cm$^{-1}$: 3050, 3020, 2930, 2855, 1600, 1505 1230. El. An. Calcd. for $C_{35}H_{36}N_2OS$: C, 78.95; H, 6.77; N, 5.27; S, 6.01. Found: C, 78.10; H, 6.60; N, 5.50; S, 6.12.

*2.3.17. 17β,20(R)-(N-Phenyl-aziridine)-20-(2-quinolinyl)-3-allyloxy-estrone (**3q**)*

Melting point = 175−178 °C (from petroleum ether 40–70 °C); $^1$H NMR ($CDCl_3$) δ: 1.29–2.30 (m, 16H), 2.8–2.9 (m, 2H), 3.81 (s, 1H), 4.42–4.56 (m, 2H), 5.20–5.42 (m, 2H), 5.80–6.0 (m, 2H), 6.70–8.36 (m, 14H); IR ($CHCl_3$) cm$^{-1}$: 3060, 3020, 2930, 2855, 1605, 1500, 1240; El. An. Calcd. for $C_{37}H_{38}N_2O$: C, 84.41; H, 7.22; N, 5.32. Found: C, 83.30; H, 7.18; N, 5.25.

## 3. Results and discussion

We studied the coupling reactions between the α-chloro-α-heteroarylalkyllithiums in Plate 1 (**1a**–**g**), acting as carbanions, and the steroids in Plate 2 (**2a**–**h**), acting as electrophiles. All the lithium-derivatives (**1a**–**g**) were prepared with LDA at −78 °C in THF from the corresponding chloroalkyl derivatives, synthesized by us if not commercially available.

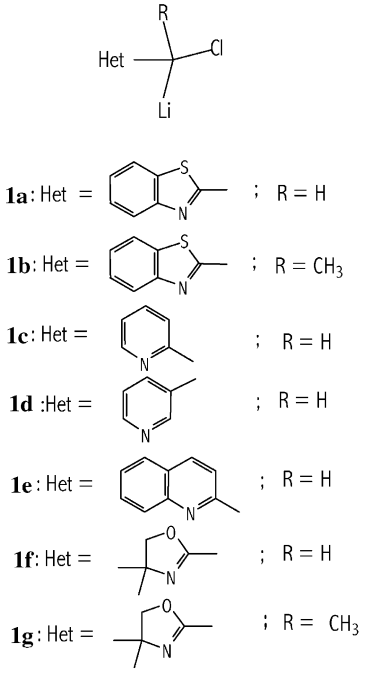



Plate 1.

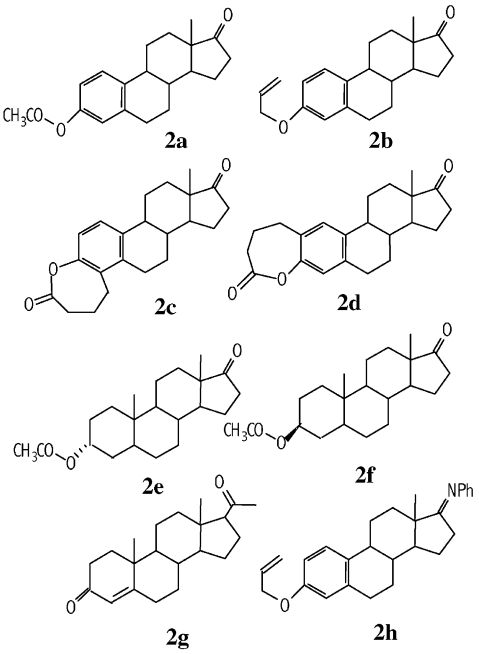
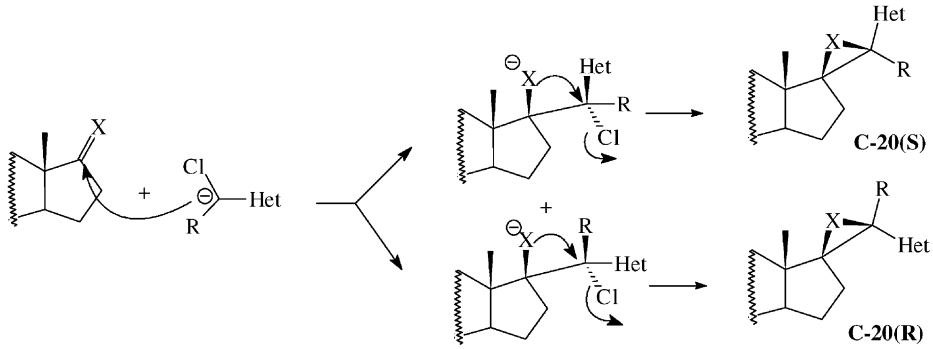



Plate 2.

For steroids also possessing an hydroxyl function, it was necessary to protect this group because it would have not permitted, for obvious reasons, the coupling with the carbanion. Protection of the hydroxyl function was accomplished, as more widely described in the experimental section, through acetylation with $Ac_2O$, by allylation with allylchloride, or by the introduction of a lactonic function between C2–3 and C3–4, according to Alper's method [20], as recently reported in one of our communications [21].

The studied reactions showed high selectivity. In fact, notwithstanding steroids **2a**, **c**–**f**, which were modified by an acetylic or lactonic function to protect the hydroxyl group and possessed two carbonylic functions, coupling with the various α-Cl-carbanions, 1**a**–**c**, **e**–**g**, always led to the isolation of an unique C-17 steroid with an oxiranyl group. The yields were good and only sometimes modest (entry 3, 4, 6, 8), Table 1. Also, in the coupling of progesterone **2g**, which has two C=O groups, with **1a**, **b**, **d**, the oxiranyl function was formed only on C-20 with quite a lot of yield (55–64%, entry 13, 14, 15). No products arising from a nucleophilic attack on C-3 were isolated.

Stereoselectivity was also found. In fact, among the various possible stereoisomers, only two and sometimes only one were found. C-20(*R*)/C-20(*S*) ratios close to unity were found in the reactions of α-Cl-heteroalkyllithium **1a**–**c**, **e** with steroids **2a**, **b**, **e**, **f**, which had the protected hydroxyl group (entry 1, 3, 4, 5, 6). A C-20(*R*)/C-20(*S*) ratio of 55/15 was observed in the coupling of the α-Cl-heteroalkyllithium **1a** with the acetyl-steroid **2e** (entry 7). In all the other cases reported in Table 1, only one diastereoisomer appeared as product of the reaction. In fact, high stereoselectivity was observed in the coupling reaction of the




Scheme 2. The α-attack of the carbanion on C-17 gives to the heteroatom (O or N) a -β-position in the functionalized steroid.

α-Cl-heteroarylalkyllithiums **1a**, **e**–**g** with the steroids **2b**–**d** (entry 2, 8–12), and of the α-Cl-heteroarylalkyllithiums **1a**, **e** with the imine **2h** (entry 16-17) which led to the isolation of only the C-20(*R*) diastereoisomer. Again, the C-20(*S*),C-21(*R*) diastereoisomer was the only product isolated from the coupling of the α-Cl-heteroarylalkyllithiums **1a**, **b**, **d** with the progesterone **2g** (entry 13, 14, 15).

As a possible explanation, we presume that the carbanion may discriminate between the two enantiotopic faces of the electrophilic carbon, leading to a α-attack (according to the commonly accepted -α- or -β-nomenclature for steroids) with smaller steric hindrance and giving a -β-position to the heteroatom of the oxido or aziridino ring (Scheme 2).

As showed elsewhere [15], the intermediate chlorohydrine (or chloroimine), which is more predominantly formed among the two possible compounds, led to the more stable form C-20(*R*) of the final oxirane or aziridine. C-20(*R*) and C-20(*S*) isomeric forms in the products with R=H were assigned by NOEs observed between undefined methylene groups and benzothiazolyl hydrogens in the first case, and between oxido or aziridino hydrogens and undefined methylene groups in the second. Analogous explanation can be presumed for the diastereoselectivity observed in the coupling reactions on the progesterone **2g**.

In conclusion, in this paper we have shown that α-halo-α-heteroarylalkyllithiums, easily available by lithiation of corresponding chloromethanes or chloroethanes, act as Darzens-type reagents and add cleanly and stereoselectively to steroids with C=O or C=N groups to give new steroid derivatives having both epoxide (or aziridine) and acetyl (or allyl or seven-membered lactone ring) functions.

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