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Stereoselective construction of a steroid 5α,7α-oxymethylene derivative and its use in the synthesis of eplerenone

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ABSTRACT

A new and practical method for a stereoselective construction of a steroid 5α,7α-oxymethylene derivative has been developed and successfully applied to the stereoselective synthesis of eplerenone (**8**). Starting with available 11α-hydroxyl canrenone (**1**), eplerenone (**8**) was synthesised in seven steps with a 48% overall yield.

During the course of a programme to develop a new approach for the synthesis of the cardiovascular drug eplerenone, an aldosterone antagonist used as an adjunct in the management of chronic heart failure, marketed by Pfizer under the trade name Inspra® [1–3], the introduction of the methoxycarbonyl substituent is the principal challenge [1,4–7]. For this purpose, we adopted a new strategy of stereroselective construction of a steroid 5α,7α-oxymethylene derivative to achieve the introduction of the methoxycarbonyl substituent. This new strategy avoided the drawbacks of prior synthetic routes, such as using toxic reagents [8,9], low stereoselectivity in substitution at C-7 position of steroids and tedious chromatographic purification of intermediates [3], etc.

Herein, a new and practical method for the stereoselective construction of a steroid 5α,7α-oxymethylene derivative via 1,6-Michael conjugate addition of steroidal 4,6-dien-3-one [10,11] and successive Tamao oxidation [12] is described and it is successfully applied to the stereoselective synthesis of eplerenone (**8**) (Scheme 1). By using the commercially available 11α-hydroxyl canrenone (**1**) as starting material, the seven-step synthetic procedure provided eplerenone (**8**) with a 48% overall yield.

1. Experimental

All melting points were determined on a Buchi 510 melting-point apparatus and were uncorrected. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were run on Bruker AM-300, Bruker AM-400 spectrometer using tetramethyl silane as the internal standard ($\delta = 0$). Splitting patterns were designated as 's, d, t, q and m'; these symbols indicated 'singlet, doublet, triplet, quartet and multiplet', respectively. Not all of the protons were reported in the ^{1}H NMR data. Mass spectra and high-resolution mass spectra were measured on a Finnigan MAT-95 mass spectrometer. Silica gel 60 H (200–300 mesh) manufactured by Qingdao Haiyang Chemical Co. (China) was generally used for chromatography. The organomagnesium reagent was Tamao reagent, which was readily prepared using the conventional method in tetrahydrofuran (THF) solution: *i*-PrOMe$_2$SiCH$_2$MgCl (1 M) [12]. The solution of CuI·2LiCl in THF (1 M) was prepared according to Ref. [13].

1.1. 11α-(Methylsulphonyl)oxy-canrenone (2)

To a solution of compound **1** (5.8 g, 16 mmol) and Et$_3$N (2.25 ml, 16 mmol) in CH_2Cl_2 (55 ml), MsCl (1.23 ml, 16 mmol) in CH_2Cl_2 (10 ml) was added dropwise with stirring at 0 °C for 2 h. The reaction mixture was quenched with water and extracted with dichloromethane (DCM). The organic layer was combined, washed with water (50 ml) and saturated brine (50 ml), dried over anhydrous sodium sulphate, filtered and concentrated. The crude product was purified by recrystallisation from petroleum/ethyl acetate to give compound **2** (6.9 g, 98%): m.p. 188–190 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 6.16 (C7–H, dd, J = 9.7, 2.2 Hz, 1H), 6.00 (C6–H, d, J = 9.7 Hz, 1H), 5.71 (C4–H, s, 1H), 5.15 (C11–H, td, J = 10.4, 4.9 Hz, 1H), 3.02 (C11–SO_3Me, s, 3H), 1.28 (C19–H, s, 3H), 1.09 (C18–H, s, 3H); ^{13}C NMR (75 MHz,$CDCl_3$) δ (ppm) 199.05, 176.00,

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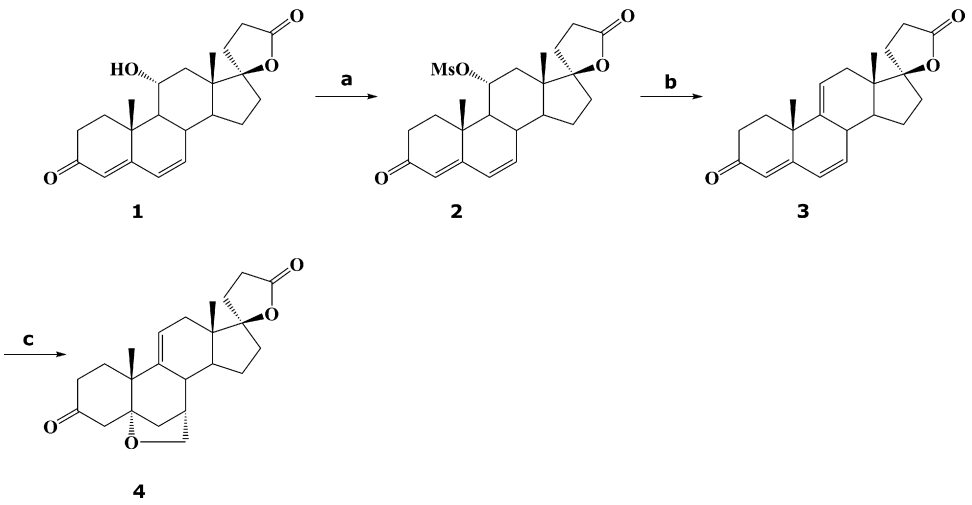


Scheme 1. Synthetic route for the ether (**4**) from 11α-hydroxy canrenone (**1**).

161.20, 137.06, 129.09, 125.53, 94.30, 77.80, 53.40, 46.43, 46.41, 40.84, 40.20, 37.60, 36.67, 35.40, 34.78, 34.23, 30.87, 29.05, 22.58, 17.19, 15.53. EI-MS (70 eV, *m*/*z*): 434 (M^+, 2%), 338 ([M−$MeSO_3H$]$^+$, 100%), 323 ([M−$MeSO_3H$−Me]$^+$, 62%).

1.2. $\Delta^{9(11)}$-Canrenone (**3**)

A mixture of formic acid (125 ml), potassium acetate (58 g, 591 mmol) and acetic anhydride (40 ml) was heated at 80 °C. After 18 h, compound **2** (10 g, 23 mmol) was added. The resulting solution was heated at 100 °C for 4 h and concentrated under reduced pressure. Ice water was added to the residue with stirring. After 20 min, the mixture was extracted with ethyl acetate (50 ml). The organic extracts were washed with cold water (50 ml), sodium bicarbonate (50 × 3 ml), water (50 ml), saturated sodium chloride (50 ml) and dried with anhydrous sodium sulphate. The solvent was removed *in vacuo* to furnish the crude product. This crude product was purified by column chromatography (petroleum ether:acetone, 4:1) to give compound **3** as a white powder (7 g, 90%): ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 6.16 (C7–H, dd, J = 9.7, 2.19 Hz, 1H), 6.09 (C6–H, dd, J = 9.7, 1.3 Hz, 1H), 5.69 (C4–H, s, 1H), 5.55–5.48 (C11–H, m, 1H), 2.93 (d, J = 11.19 Hz, 1H), 1.30 (C19–H, s, 3H), 0.99 (C18–H, s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 199.07, 176.36, 161.83, 140.33, 137.85, 127.26, 123.90, 118.501, 94.79, 44.28, 43.96, 38.84, 38.54, 35.21, 34.02, 32.88, 32.02, 31.17, 29.08, 24.35, 22.88, 14.32. EI-MS (70 eV, *m*/*z*): 338 (M^+, 100%), 323 ([M−Me]$^+$, 57%), 305([M−Me−H_2O]$^+$, 12%).

1.3. 17β-Hydroxy-7α-methylene-5α-oxo-pregna-4,9(11)-dien-3-one-21-carboxylic acid, γ-lactone (**4**)

To a solution of CuI·2LiCl (100 ml, 100 mmol) in THF, *i*-$PrOMe_2SiCH_2MgCl$ (100 ml, 100 mmol) in THF was added dropwise at −68 °C with vigorous stirring. After 10 min, $BF_3{\cdot}OEt_2$ (12.6 ml, 100 mmol) was added dropwise. After 1 h, a solution of compound **3** (8.45 g, 25 mmol) in 25 ml THF was added dropwise to the black brown reaction mixture. After 10 h, the reaction mixture was cooled to 0 °C, and was quenched with HCl aqueous solution (5%, w/w) and extracted with CH_2Cl_2 (3 × 50 ml). The combined organic layers were filtered, washed with water (3 × 100 ml) and saturated brine, dried over anhydrous sodium sulphate, filtrated and concentrated. The above residue was diluted with THF/MeOH (100 ml/100 ml), and then $KHCO_3$ (10 g, 100 mmol) and KF (11.6 g, 200 mmol) were added. To the stirred mixture, H_2O_2 (30%, w/w) (160 ml) was added in one portion. The reaction mixture was stirred at 40–50 °C for 4 h, then at room temperature (r.t.) for 10 h, quenched with a saturated Na_2SO_3 solution (10 ml) over 30 min, and filtered. The filtrate and washes were combined and concentrated. The residue was diluted with EtOAc, washed with saturated brine, dried over magnesium sulphate, filtered and concentrated. The crude product was purified by column chromatography (petroleum ether:acetone, 4:1) to give compound **4** (6.3 g, 71%): m.p. 200–202 °C; $[\alpha]^{17}{}_D$: −22° (c 0.1, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.57–5.48 (m, 1H), 3.70 (dd, J = 8.0, 4.2 Hz, 1H), 3.60 (d, J = 8.0 Hz, 1H), 2.81 (d, J = 15.0 Hz, 1H), 1.27 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 209.69 (q), 176.54 (q), 142.82 (q), 120.25 (t), 95.26 (q), 87.90 (q), 69.09 (d), 47.96 (d), 44.10 (q), 43.12 (q), 43.04 (t), 42.39 (t), 40.36 (d), 38.29 (t), 37.55 (d), 35.37 (d), 32.99 (d), 32.94 (d), 31.49 (d), 29.20 (d), 23.96 (s), 23.27 (d), 14.40 (s); EI-MS (70 eV, *m*/*z*): 370 (M^+, 38%), 355 ([M−Me]$^+$, 7%), 271 (64%), 124 (100%), 137 (85%).

1.4. 17β-Hydroxy-7α-(1′-hydroxy)methylene-5α-oxo-pregna-4,9(11)-dien-3-one-21-carboxylic acid, γ-lactone (**5**)

Methyltrifluoromethyldioxirane [14] was bubbled into the solution of compound **4** (120 mg, 0.32 mmol) in CH_2Cl_2 (50 ml) at −25 °C for 2 h. The solvent was removed *in vacuo* to furnish the crude product. This crude product was purified by column chromatography (petroleum ether:EtOAc, 1:1) and recrystallised from acetone/CH_2Cl_2 to give colourless, transparent crystalline compound **5** (111 mg, 90%): m.p. 260–262 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.55–5.45 (C11–H, m, 1H), 5.01 (C5–OCH–, s, 1H), 3.04 (C5–OCHOH–, brs, 1H), 2.84 (C4–H, d, J = 15.18 Hz, 1H), 1.28 (C19–H, s, 3H), 0.91 (C18–H, s, 3H); ^{13}C NMR (100 MHz,$CDCl_3$) δ (ppm) 209.64 (q), 176.58 (q), 142.65 (q), 120.38 (t), 95.20 (q), 90.25 (q), 98.31 (t), 48.44 (d), 44.20 (q), 42.80 (q), 44.54 (t), 42.09 (t), 37.48 (d), 41.18 (t), 37.13 (d), 35.32 (d), 33.08 (d), 32.93 (d), 31.43 (d), 29.18 (d), 23.38 (s), 23.38 (d), 14.17 (s); EI-MS (70 eV, *m*/*z*): 386 (M^+, 7%), 368 ([M−H_2O]$^+$, 44%), 353 (28%), 371 (12%), 124 (100%).

1.5. 5α,17β-Dihydroxy-3-oxo-pregn-9(11)-ene-7α,21-dicarboxylic acid, bis-γ-lactone (**6**)

To a suspension of the lactol **5** (31 mg, 0.08 mmol) and molecular sieves 4A (120 mg) in anhydrous CH_2Cl_2 (0.5 ml) pyridinium dichromate (60 mg, 0.16 mmol) was added. The mixture was stirred overnight at room temperature, diluted with n-hexane/ethyl acetate (4/1, v/v), and filtered through a pad of silica gel. The filtrate was concentrated under reduced pressure and recrystallised from acetone to give crystalline **6**[3] (28 mg, 98%): m.p. 256–258 °C;

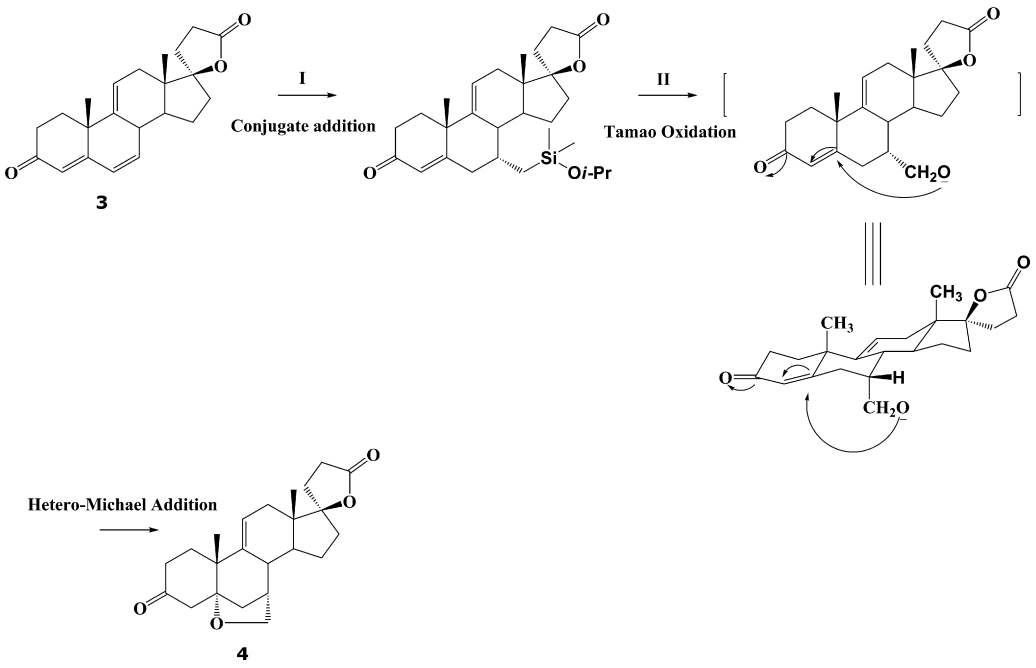


Fig. 1. 1.6-Michael conjugate addition and successive Tamao oxidation.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.72–5.66 (C11–H, m, 1H), 2.78 (C4–H, d, J = 16.3 Hz, 1H), 1.40 (C19–H, s, 3H), 0.94 (C18–H, s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 206.08 (q), 176.53 (q), 139.54 (q), 124.07 (t), 94.91 (q), 90.97 (q), 175.45 (q), 47.10 (d), 43.91 (q), 41.55 (q), 42.36 (t), 41.60 (t), 38.96 (d), 41.06 (t), 37.00 (d), 35.17 (d), 33.00 (d), 32.41 (d), 31.40 (d), 29.15 (d), 23.03 (s), 23.12 (d), 14.26 (s); EI-MS (70 eV, m/z): 384 (M^+), 124 (50%), 57 (100%).

*1.6. 17β-Hydroxy-7α-carbomethoxy-3-oxo-pregna-4,9(11)-diene-21-carboxylic acid, γ-lactone (**7**)*

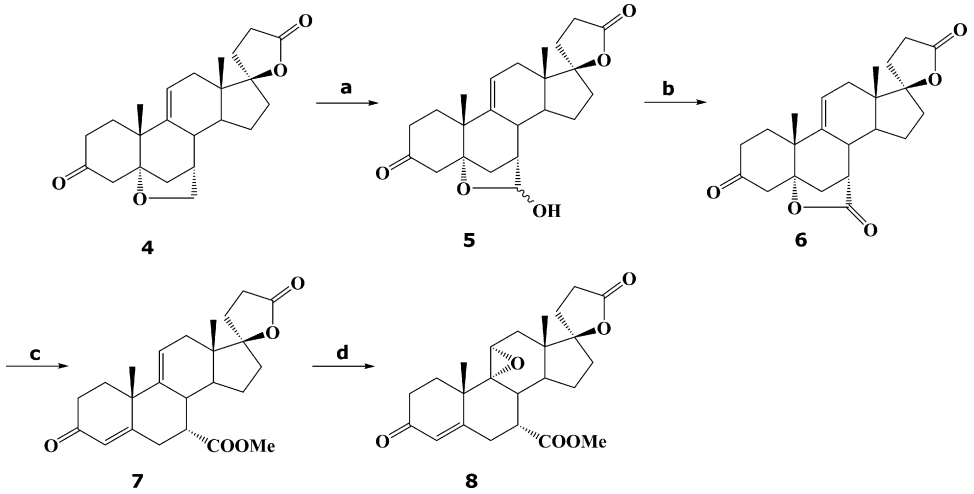
Compound **7** was prepared according to Refs.: [3,9] ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.72 (C4–H, s, 1H), 5.65 (C11–H, d, J = 5.30 Hz, 1H), 3.59 (C7–COOMe, s, 3H), 2.99 (s, 1H), 2.83 (dd, J = 15.03, 5.18 Hz, 1H), 1.40 (C19–H, s, 3H), 0.95 (C18–H, s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 198.81, 176.67, 172.83, 166.86, 142.50, 125.87, 119.13, 95.25, 51.61, 44.64, 43.94, 43.25, 40.72, 40.53, 35.90, 35.59, 34.36, 33.91, 33.07, 31.62, 29.38, 27.35, 23.45, 14.23. EI-MS (70 eV, m/z): 398 (M^+, 100%), 383 ([M−Me]$^+$, 84%).

*1.7. Eplerenone (**8**)*

Compound **8** was prepared according to the Ref.: [3] m.p.: 242–244 °C (Ref. [9] 240–242 °C); $[\alpha]^{24}{}_D$: +1.2° (c 1.0, $CHCl_3$) (lit. [9] $[\alpha]_D$: +5° (c 0.437, $CHCl_3$)); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.89 (s, 1H), 3.64 (s, 3H), 3.11 (d, J = 5.16 Hz, 1H), 2.87 (dd, J = 7.30, 4.19, 1H), 1.01 (s, 3H), 1.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 198.00, 176.25, 172.58, 164.99, 127.09, 94.57, 65.32, 51.61, 51.49, 43.86, 41.29, 39.73, 38.76, 37.27, 34.98, 34.84, 33.09, 31.03, 30.95, 28.95, 26.98, 22.32, 22.15, 16.23; EI-MS (70 eV, m/z): 414 (M^+), 399 ([M−Me]$^+$), 396 ([M−H_2O]$^+$), 355 ([M−COOMe]$^+$).

2. Results and discussions

With regard to the stereochemical result of conjugate addition of organometallic reagents to various steroidal 4,6-dien-3-ones [10], we envisioned that the approach of the relatively bulky (isopropoxydimethylsilyl)methyl anion to the C(6)=C(7) bond of



Scheme 2. Synthetic route for eplerenone (**8**) from the ether (**4**).

4,6-dien-3-one would occur from the slightly less hindered α-side, resulting in a predominant product with the functional methylene group having the desired 7α-configuration. Therefore, the stereoselective construction of a steroid 5α,7α-oxymethylene derivative was designed via 1,6-Michael addition and Tamao oxidation (Fig. 1).

The stereoselective synthesis of the ether (**4**) is illustrated in Scheme 1. The known mesyltate (**2**) was prepared by mesylation of the commercially available 11α-hydroxy canrenone (**1**) and subjected to the elimination to provide the desired $\Delta^{9(11)}$-canrenone (**3**) in 90% yield [15]. Attempts at 1,6-Michael addition of $\Delta^{9(11)}$-canrenone (**3**) with *i*-$PrOMe_2SiCH_2MgCl/CuI{\cdot}2LiCl$ or *i*-$PrOMe_2SiCH_2MgCl/CuBr{\cdot}Me_2S$ initially failed to provide the desired addition product. This problem was, however, overcome by effecting the stereoselective conjugate addition process in the presence of $BF_3{\cdot}OEt_2$ [11]. Subsequent Tamao oxidation [16] yielded the required ether (**4**) in a 71% yield.

We next focussed attention on using the ether (**4**) in the synthesis of eplerenone (**8**). However, initial oxidation of the ether moiety of compound (**4**) by chromic acid [17] or $RuCl_3/NaIO_4$ [18] failed, regardless of altering conditions, such as the pH value, temperature and solvent. We then turned to other oxidising agents and fortunately found that, methyltrifluoromethyldioxirane or dimethyldioxirane could regioselectively oxidate compound (**4**) to the corresponding product (**5**) with an excellent yield (90%) [14]. The latter (**5**) was converted to the lactone (**6**) on further oxidation [19]. The esterification of lactone (**6**) with dimethyl sulphate provided the enester (**7**). Finally, epoxidation of the enester (**7**) yielded the target product (**8**) (Scheme 2) [3].

In conclusion, we succeeded in the stereoselective construction of a steroid 5α,7α-oxymethylene derivative from 11α-hydroxyl canrenone (**1**) and applied this method to the synthesis of eplerenone (**8**) with a 48% overall yield in seven steps.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.steroids.2010.08.009.

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