Steroids 77 (2012) 1086–1091

Contents lists available at SciVerse ScienceDirect

Steroids

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

A diastereoselective synthesis of 7α-nitromethyl steroid derivative and its use for an efficient synthesis of eplerenone

Bin Zhang, Hongli Chen, Huanyu Tang, Huijin Feng, Yuanchao Li *

Shanghai Institute of Materia Medica, Chinese Academy of Science, 555 Zu Cong Zhi Road, Zhangjiang Hi-Tech Park, Shanghai 201203, PR China

ARTICLE INFO

Article history:
Received 3 February 2012
Received in revised form 13 April 2012
Accepted 16 April 2012
Available online 12 May 2012

Keywords:
Nitromethane
Eplerenone
1,6-Conjugated addition
Quaternary ammonium salt
Synthesis

ABSTRACT

A novel and efficient method of stereoselectively introducing α-nitromethyl group to C-7 position of 11α-hydroxyl canrenone **4** was described. In addition, this method was successfully applied in a total synthesis of Eplerenone **8**. The route was characteristic of simple operation, moderate reaction conditions with 5 steps and 55% total yield, at the same time, without any expensive or toxic reagent in use.

© 2012 Elsevier Inc. All rights reserved.

1. Introduction

The reagent nitromethane or its derivatives have been used in steroid chemistry to introduce C-7 nitromethyl group by 1,6-conjugated addition to steroidal 4,6-dien-3-one. However, to our knowledge, only the corresponding 7β-nitromethyl steroid derivatives **1**, **2** [1,2] and nitromethylene **3** [3] were reported (Fig. 1). When compound **4** was treated with NaOMe/$MeNO_2$/H_2O in DMF at room temperature for 1 day [2,3], the conjugated addition gave a mixture of compound **5α** and **β** with poor stereoselectivity (α/β = 1.6:1) and very low yield (trace). This result intrigued us to optimize the reaction conditions and developed a novel method to stereoselectively introduce 7α-nitromethyl group, for the 7α-nitromethyl group on steroid **5α** was very easy to be converted into carboxy by Nef reaction without the corresponding configuration changing [4–6]. The idea to apply steroid **5α** in a synthesis of eplerenone also impelled us to optimize reaction conditions.

Eplerenone is cardiovascular drug, an aldosterone antagonist used as an adjunct in the management of chronic heart failure, marketed by Pfizer under the trade name Inspra [7]. In the total synthesis of eplerenone, the most principal challenge was the introduction of the carbomethoxy substituent. In 1984, Grob accomplished the first synthesis of eplerenone by employing Nagata hydrocyanation of $\Delta^{9(11)}$-canrenone as the key step [8], but with moderate stereoselectivity, tedious column chromatography and using toxic cyanide. After that, many companies and research groups were eager to install carbomethoxy group at C-7 by a convenient method in the total synthesis of eplerenone. In 1997, John Ng used toxic acetone cyanohydrin to construct enamine bridge at C4 and C7, and then converted it to carbomethoxy [9]. 6 years later, Pearlman developed a new approach to the furan degradation [10] and used it in the synthesis of eplerenone with higher yield and better selectivity, but this approach needed as low as −50 °C and five steps to degrade furan, which was not atom efficient and problematic in industrial use. Recently, Wuts chose dehydroepiandrosterone as start material by allylic substitution at C7 with moderate stereoselectivity by using expensive stoichiometric amount transition metal salt and an inert environment [11,12]. In 2011, our group developed a new and practical method for the stereoselective construction of a steroid 5α,7β-oxymethylene derivative via 1,6-Michael conjugate addition of steroidal 4,6-dien-3-one at as low as −68 °C and applied it in the synthesis of eplerenone [13].

We finally found, when **4** was treated with K_2CO_3/$MeNO_2$ in DMF in the presence of a catalytic amount of octadecyl dimethyl benzyl ammonium chloride at 90 °C for two days, it was result in 1,6-conjugated addition and a stereochemical conversion at C-7 position in one step to afford the 7α-nitromethyl steroid **5α** with 90% yield and 96% *de* (Scheme 1). With compound **5α** in hand, we succeeded in a total synthesis of Eplerenone **8** with 5 steps and 55% total yield.

2. Experimental

All melting points were determined on a Büchi 510 melting point apparatus and were uncorrected. ^1H and ^{13}C NMR spectra

* Corresponding author. Tel.: +86 21 50806600x3502; fax: +86 21 50807288.
E-mail address: ycli@mail.shcnc.ac.cn (Y. Li).

0039-128X/$ - see front matter © 2012 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.steroids.2012.04.017

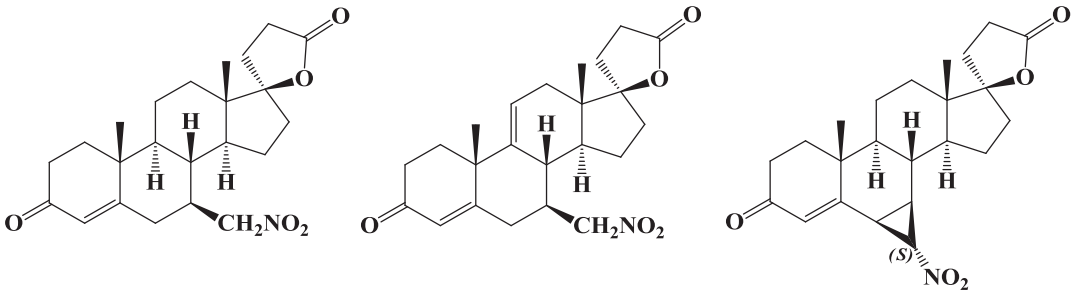


Fig. 1. 7β-Nitromethyl-4,5-dihydrocanrenone; 7β-nitromethyl-$\Delta^{9(11)}$-4,5-dihydrocanrenone and 6β,7β-methylene-(1′S)-nitro-3-oxo-17α-pregn-4-en-21-carboxylic acid, γ-lactone.

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. X-ray crystallographic data were obtained on a CAD-4 diffractometer. Optical rotations were recorded on a Jasco-Dip-181 polarimeter. Mass spectra and high-resolution mass spectra were measured on a Finnigan MAT-95 mass spectrometer. High performance liquid chromatograms (HPLC) were taken on Agilent 1100 instruments and Waters 2998 with column Venusii MP™ C18, 5 μm, 100 Å, 10 × 250 mm and SunFine™ C18, 5 μm,4.6 × 150 mm. Silica gel 60 H (200–300 mesh) manufactured by Qingdao Haiyang Chemical Co. (China) was generally used for chromatography. N,N-dimethyl formamide (DMF) and $MeNO_2$ were distilled and dried by 4 Å molecular sieves overnight. K_2CO_3 was well ground into a powder, baked at 145 °C for 10 h and then cooled in desiccator with P_2O_5. TMG, TEA and DIPEA were short for trimethylglycine, triethyl amine and N,N-Diisopropylethylamine, respectively. The purity of each step product was >98%, which was determined by HPLC and H NMR.

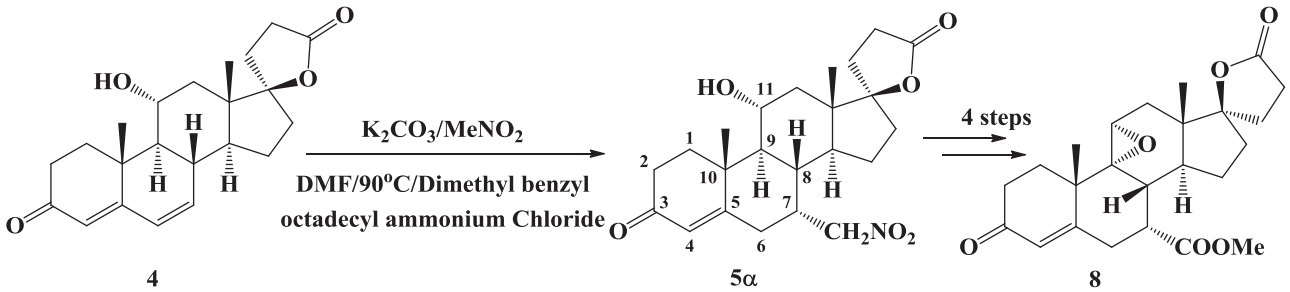
*2.1. 11 β,17β-Dihydroxy-7α/β-nitromethyl-pregna-4-en-3-one-21-carboxylic acid, γ-lactone (**5α** and **β**)*

To a solution of compound **4** (1.07 g, 3 mmol) in $MeNO_2$ (10 ml), 1,8-Diazabicyclo [5.4.0] undec-7-ene (DBU) (0.8 ml, 5.3 mmol) was added at room temperature and stirred overnight. The resulting reaction was quenched by a.q. HCl (10% w/w) to adjust the pH to 6. Then solvent was removed under vacuum and the residue was purified by silica column chromatography eluted with EtOAc/cyclohexane (1:4, v/v) to afford diastereomers **5α** (308 mg, 25% yield) and **β** (192 mg, 15% yield). The compound **5α** was readily recrystallized from EtOAc to afford colorless crystals.Compound **5α**: mp:281–282 °C; [α]20D: 51° (c 0.24, $CHCl_3$); IR ν_{max}(KBr) 3467, 2950, 1766, 1662, 1550, 1458, 1441, 1419, 1382, 1344, 1274, 1192; UV_{max}: 242 nm; ^1H NMR (300 MHz,$CDCl_3$) δ5.82 (s, 1H), 4.38–4.20 (m, 2H), 4.10 (tt, *J* = 10.29, 10.29, 4.95, 4.95 Hz, 1H), 2.81 (td, *J* = 13.99, 4.16, 4.16 Hz, 1H), 2.73–2.27 (m, 10H), 2.07–1.70 (m, 7H), 1.68–1.59 (m, 2H), 1.50 (ddd, *J* = 24.57, 12.19, 5.69 Hz, 1H), 1.38 (s, 3H), 1.04 (s, 3H); ^{13}C NMR(100 MHz,$CDCl_3$) δ 199.092, 176.239, 164.980, 128.330, 94.707, 74.029, 68.710, 53.387, 46.162, 45.170, 43.219, 39.867, 37.704, 37.471, 36.477, 35.951, 35.328, 34.207, 31.127, 29.087, 22.276, 18.343, 15.679; EI MS(70 eV, m/z): 417(M^+, 21%), 399(17%), 370(44%), 111(100%); HR-MS(EI) calcd for $C_{23}H_{31}NO_6$(M^+) 417.2151, Found 417.2153; *Anal.* Calc. for $C_{23}H_{31}NO_6$: C, 66.17; H, 7.48; N, 3.35. Found: C, 66.35; H, 7.63; N, 3.31%.

Compound **5β**: ^1H NMR (300 MHz,$CDCl_3$) δ 5.73 (s, 1H), 4.73 (dd, *J* = 12.72, 3.72 Hz, 1H), 4.37 (dd, *J* = 12.51, 7.64 Hz, 1H), 4.15–3.99 (m, 1H), 2.67–1.37 (m, 21H), 1.35 (s, 3H), 1.03 (s, 3H); ^{13}C NMR(100 MHz,$CDCl_3$) δ199.556, 176.137, 166.179, 125.006, 93.623, 80.058, 68.297, 58.043, 47.763, 47.027, 43.126, 41.537, 39.625, 38.306, 37.275, 37.004, 35.457, 34.181, 30.969, 29.052, 26.114, 18.600, 16.023; UV_{max}: 243 nm; EI MS(70 eV, m/z):417(M^+, 17%), 111(100%), 370(37%); HR-MS(EI) calcd for $C_{23}H_{31}NO_6$(M^+) 417.2151, found 417.2157.

*2.2. 11 β,17β-dihydroxy-7α-nitromethyl-pregna-4-en-3-one-21-carboxylic acid, γ-lactone (**5α**)*

To a solution of compound **4** (20 g, 56 mmol), octadecyl dimethyl benzyl ammonium chloride (2.32 g, 6 mmol) and $MeNO_2$ (60 ml, 1120 mmol) in DMF (190 ml) equipped with a $CaCl_2$ drying tube and a reflux condenser, K_2CO_3 (78 g, 565 mmol) was added at 90 °C with stirring. The mixture was stirred at this temperature for 48 h. The resulting mixture was cooled to room temperature, and then filtered. The filter cake was washed with dichloride methane (DCM) for three times. The organic layers were combined with the filtrate, and adjusted pH to 6 with a.q. HCl (10%, w/w). The HPLC



Scheme 1. Synthesis of **5α** and its application in synthesis Eplerenone **8**.

analysis suggested the ratio of diastereomer **5α** to **β** was 48:1. The combined organic layers were concentrated under vacuum to give crude product as brown solid. The crude product was washed with water three times and then filtered. The residue was diluted with DCM, and then filtered. The filtrate was washed with a.q. HCl (10%, w/w), brine and dried by Na_2SO_4 to afford crude powder product **5α** (23 g), which was used directly for next step without purification. The crude was readily recrystallized from EtOAc to afford pure product **5α** (21 g, 90% yield).

2.3. 11 β,17β-dihydroxy-7α- methoxycarbonyl -pregna-4-en-3-one-21-carboxylic acid, γ-lactone (**6**)

To a solution of **5α** (5 g, 12 mmol) in DMF (40 ml), AcOH (2.9 ml, 51 mmol) was added at 45 °C with stirring. 30mins later, $NaNO_2$ (2.484 g, 36 mmol) was slowly added in batches to the mixture. 1 h later, a solution of AcOH (2.9 ml, 51 mmol) in DMF (3 ml) was added dropwise to the mixture. After 4 h, the reaction was cooled to 0 °C and then quenched by sat. Na_2SO_3 solution (54 ml, 89 mmol). It was allowed to warm to room temperature and stirred overnight. The solvent was removed completely under vacuum to give powder solid. The solid was diluted with acetone and filtered. The filter cake was washed with acetone for three times. The organic layers were combined with filtrate and then concentrated to 100 ml. To the result solution, MeI (1.5 ml, 24 mmol) and K_2CO_3 (5 g, 36 mmol) were added at 0 °C. The mixture was allowed to warm to room temperature and stirred overnight. The mixture was filtered and the filter cake was washed with DCM for three times. The organic layers were combined with filtrate and then the solvent was completely removed. The residue was diluted with DCM and washed with a.q HCl (10%, w/w), sat. $NaHCO_3$, brine and dried by Na_2SO_4, then filtered and the filtrate was concentrated to afford crude product **6**, which could be purified by recrystallization from DCM/toluene to afford colorless crystals **6** (4 g, 80% yield) [14]: mp.:230–232 °C; ^{1}H NMR (300 MHz,$CDCl_3$) δ 5.68 (s, 1H), 4.04 (dt, *J* = 10.23, 9.84, 3.98 Hz, 1H), 3.64 (s, 3H), 2.85–2.71 (m, 2H), 2.68–2.18 (m, 8H), 2.10–1.57 (m, 9H), 1.49–1.40 (m, 2H), 1.35 (s, 3H), 1.00 (s, 3H); HR-MS(EI) calcd for $C_{24}H_{32}O_6$ (M^+) 416.221 found 416.225; *Anal.* Calc. for $C_{24}H_{32}O_6$: C,69.21, H,7.74. Found: C, 68.32; H, 7.72%. UV_{max}: 244 nm.

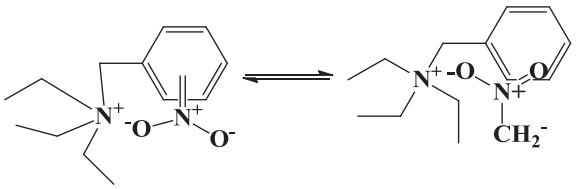


Fig. 2. Ionic bond and π–π stacking interaction.

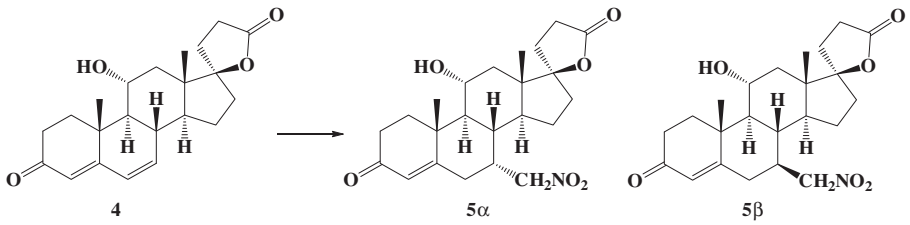
2.4. 17β-Hydroxy-7α-carbomethoxy-3-oxo-pregna-4,9(11)-diene-21-carboxylic acid, γ-lactone (**7**)

Compound **7** was prepared from **6** according to the reference [12]. mp.: 204–2061 °C; ^{1}H NMR (300 MHz,$CDCl_3$) δ 5.67 (s, 1H), 5.60 (d, *J* = 5.84 Hz, 1H), 3.54 (s, 3H), 2.93 (dd, *J* = 4.48, 2.00 Hz, 1H), 2.78 (ddd, *J* = 14.93, 5.15, 1.64 Hz, 1H), 2.61–2.36 (m, 6H), 2.33–2.05 (m, 5H), 1.99–1.75 (m, 4H), 1.51–1.38 (m, 2H), 1.35 (s, 3H), 0.90 (s, 3H); ^{13}C NMR(100 MHz,$CDCl_3$) δ 198.805, 176.667, 172.828, 166.858, 142.504, 125.871, 119.134, 95.252, 51.605, 44.638, 43.935, 43.250, 40.719, 40.526, 35.902, 35.586, 34.359, 33.912, 33.068, 31.616, 29.378, 27.354, 23.448, 14.234.

2.5. Eplerenone (**8**)

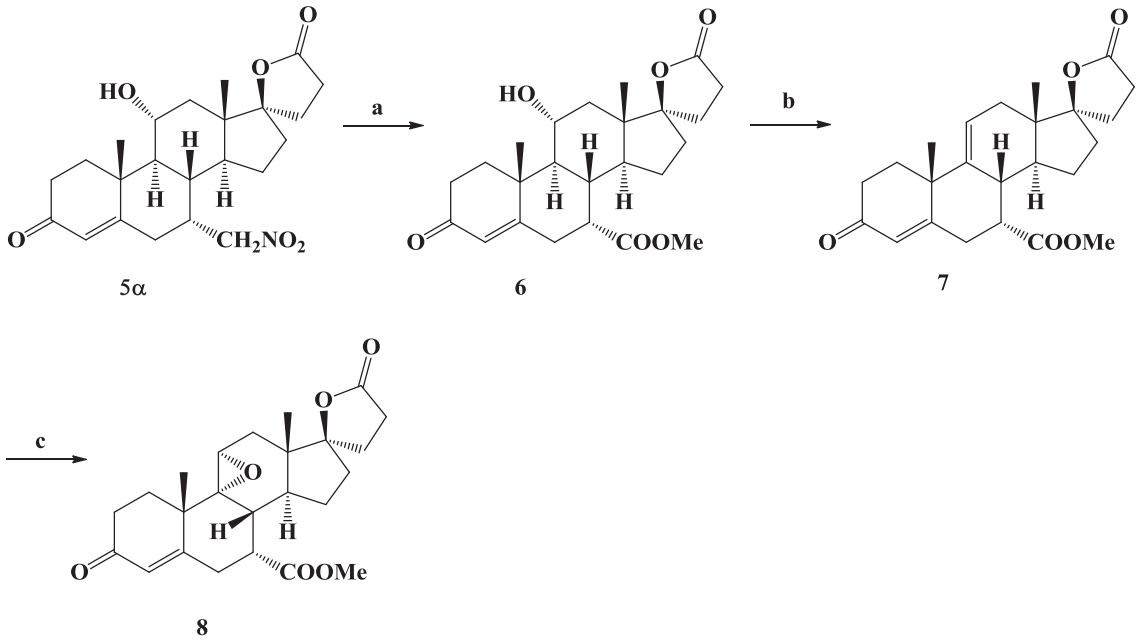
Compound **8** was prepared from **7** according to the reference [10]. [α]20D:+2.2°(c 0.415, $CHCl_3$) (lit. [8] [α] = +5° (*c* = 0.437, $CHCl_3$)); mp. 242–244 °C (lit. [8] 240–242 °C); UV_{max}: 240 nm; *Anal.* Calc. for $C_{24}H_{30}O_6$: C,69.54; H,7.30. Found: C, 69.25; H, 7.30%. X-ray data of Eplerenone **8** was included in Supplementary data.

Table 1
1,6-Conjugated addition of $MeNO_2$ to dienone **4**.



Entry	Base	Catal.	Sol.	Temp. (°C)	Time (h)	Yield (%)[a]	α:β[b]
1	NaOMe	–	DMF	RT	9	Trace	1.6:1
2	K_3PO_4	A[c]	DMF	RT	9	5	1.6:1
3	K_3PO_4	A	DMF	40	9	60	4:1
4	K_3PO_4	A	DMF	80	6	50	5:1
5	K_2CO_3	A	DMF	90	9	80	5:1
6	K_3CO_3	B[d]	DMF	90	9	30	1:1
7	K_2CO_3	A	DMF	90	48	88	10:1
8	K_2CO_3	C[e]	DMF	90	48	90	48:1

[a] The yields were determined by column chromatography purification.
[b] The ratios of crude products were determined by HPLC and ^{1}H NMR.
[c] A was benzyl triethyl ammonium chloride (10% mol).
[d] B was tetraethyl ammonium chloride (10% mol).
[e] C was octadecyl dimethyl benzyl ammonium chloride (10% mol).



Scheme 2. Compound **5** was used in synthesis of Eplerenone **8**. Reagents and conditions: (a) (1) $NaNO_2$/DMF/AcOH, 35–40 °C; (2) K_2CO_3/MeI/acetone, RT; (b) (1) MsCl/Et_3N/CH_2Cl_2, 0 °C; (2) HCOOK/HCOOH/Ac_2O, 100 °C; (c) Cl_3CCONH_2/H_2O_2 (30% w/w)/CH_2Cl_2/K_2HPO_4, 10–20 °C.

*2.6. The convertion of compound **5β** into **5α***

To a solution of compound **5β** (1 g, 2.4 mmol), octadecyl dimethyl benzyl ammonium chloride (93 mg, 0.22 mmol) and $MeNO_2$ (2 ml, 37 mmol) in DMF (6 ml) equipped with a $CaCl_2$ drying tube and a reflux condenser, K_2CO_3 (3.3 g, 24 mmol) was added at 90 °C with stirring. The mixture was stirred at this temperature for 48 h. The resulting mixture was cooled to room temperature, and then filtered. The filter cake was washed with dichloride methane (DCM) for three times. The organic layers were combined with the filtrate and all the solvent was removed under reduced pressure to afford crude product **5α**. There was no compound **5β** in crude product detected by HPLC and H NMR. The crude product was placed under vacuum to afford brown powder. The crude powder product was washed with water in sonic washing machine and then filtered for three times. The residue was readily recrystallized from EtOAc to afford pure product **5α** (980 mg, 98% yield).

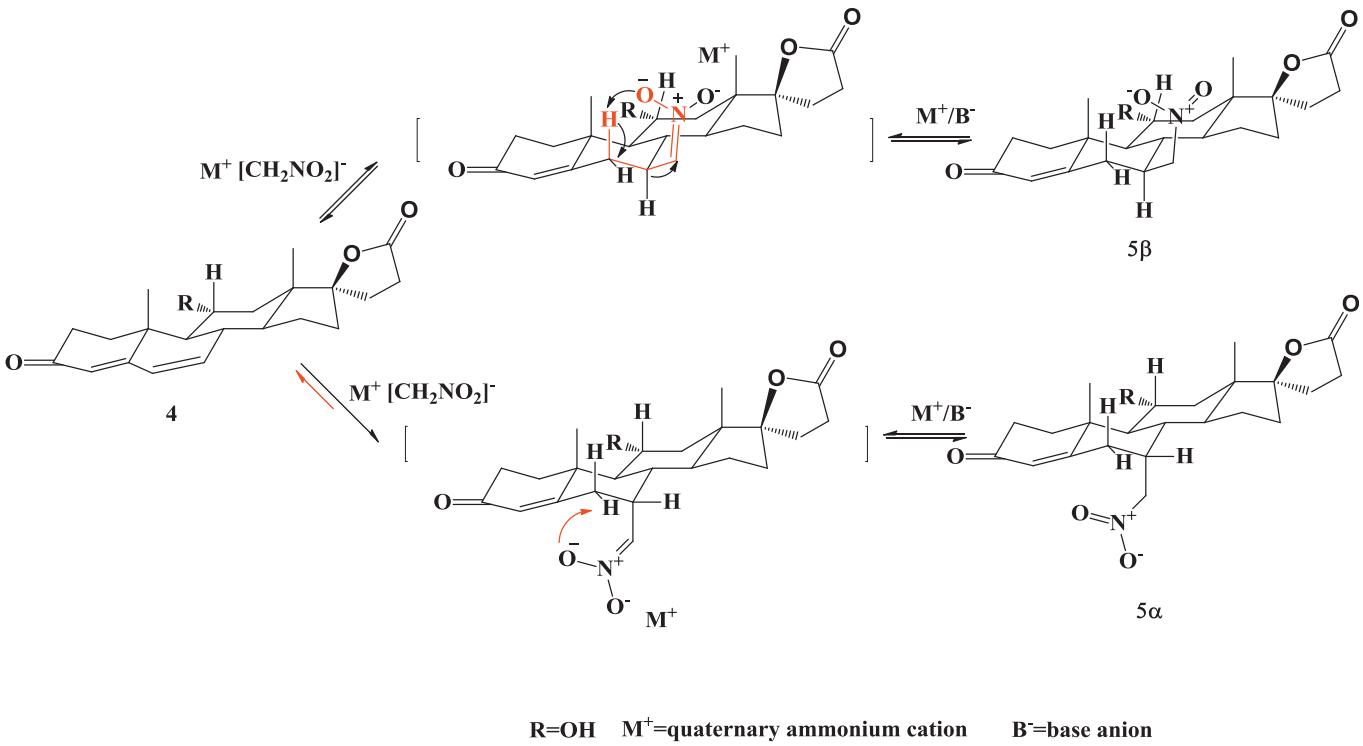


Fig. 3. The mechanism of stereochemical conversion of a steroid 7β-nitromethyl derivative into 7α.

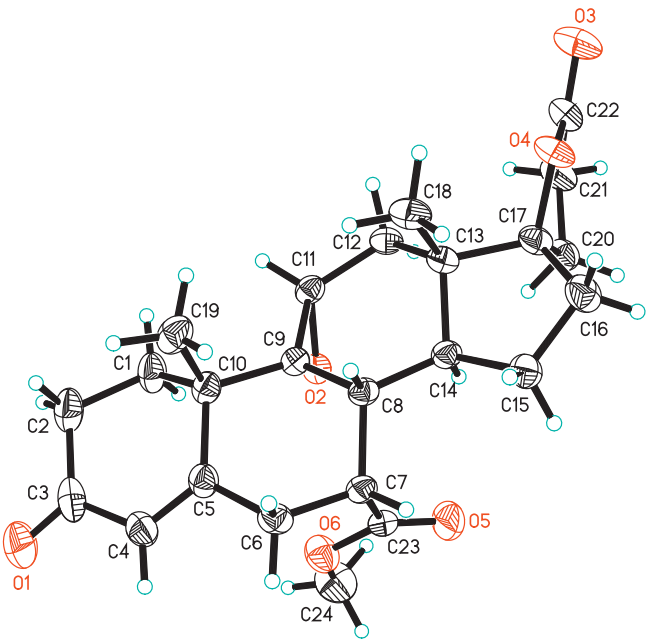


Fig. 4. X-ray crystallographic structure of Eplerenone **8**.

3. Results and discussions

Our synthetic efforts began with preparation of 7α-nitromethyl canrenone by using commercial 11α-hydroxy canrenone **4** as the starting material. The results of 1,6-conjugated addition to 11α-hydroxy canrenone **4** in different conditions are summarized in Table 1. Because NaOMe (5 eq.)/$MeNO_2$ (11 eq.)/H_2O (11 eq.) in DMF at room temperature were found as the most frequently used conditions, it was initially employed (entry 1). Indeed, under these conditions, there were trace amounts of compound **5α** and **β** found. We tried to increase the reaction temperature. But when it was as high as 50 °C, the reaction became complex. A lot of $NaCH_2NO_2$ was precipitated from the solution when NaOMe was added, and HPLC analysis indicated there was no compound **5α** or **β** detected even for 2 days if without water adding. We thought water helped make $NaCH_2NO_2$ dissolve in DMF. Different solvents were screened, such as nonpolar and polar ones and different bases, including organic and inorganic bases, but all failed.

Quaternary ammonium salts were usually used in improving $MeNO_2$ conjugate addition to α,β-unsaturated ketone [15,16]. The pre-transition state of the enantioselective Michael addition of nitromethane to ketone catalyzed by a chiral quaternary ammonium salts was described by Corey [17]. We envisioned the benzyl group or $ArCH_2$-substituent was necessary in quaternary ammonium salt to improve the nucleophilicity of nitromethane anion by ionic bond and a π–π stacking interaction [18] between benzyl group and nitromethane anion (Fig. 2).

The commercially available benzyl triethyl ammonium chloride was chose as the phase transfer catalyst at very beginning. Increasing reaction temperature could significantly improve the yield and slightly improve the diastereomeric ratio (entry 2 and 3). But when the temperature was increased to higher than 80 °C in the presence of K_3PO_4, the reaction became complex and the yield was obviously decreased even in 6 h (entry 4). So we turned to much weaker bases, such as K_2HPO_4, $KHCO_3$, CsF etc., and found reaction proceed with better yield only in the presence of K_2CO_3 at 90 °C (entry 5). The reaction time was another key factor effecting on the stereoselectivity. A longer extension time could dramatically increase the diastereomeric ratio and slightly improve the yield (entry 7). The structure of quaternary ammonium salts also had effect on the yield and the stereoselectivity. A quaternary ammonium salts containing benzyl group was required to ensure the better yield and the better stereoselectivity. There was screening of many commercial alkyl quaternary ammonium salts. For examples, tetrabutyl ammonium bromide, methyl trioctyl ammonium chloride or stearyl trimethyl ammonium chloride gave moderate yield and poor stereoselectivity similarly as tetraethylammonium chloride did (entry 6). We finally found the bulky commercial benzyl quaternary ammonium salts, such as octadecyl dimethyl benzyl ammonium chloride, was the best phase transfer catalyst. Compound **4** with $MeNO_2$ and K_2CO_3 under catalysis of octadecyl dimethyl benzyl ammonium chloride (10% mol) at 90 °C afforded compound **5α** in satisfactory yield (90%) and good *de* (96%) (entry8).

We envisioned the mechanism of stereochemical inversion of 7β-nitromethyl group into more thermodynamically stable 7α one was that the elimination of nitromethane from compound **5β** was much more easily than that from compound **5α**. The formation of six-membered-ring pre-transition state accounted for preferred elimination of nitromethane from compound **5β** at high temperature (Fig. 2). The exclusive formation of compound **5α** was quite likely the result of a thermodynamic control. It was supported by the fact when compound **5β** was treated with $MeNO_2$, K_2CO_3 and octadecyl dimethyl benzyl ammonium chloride (10% mol) at 90 °C for 2 days, which were the same conditions as entry 8 showed, compound **5β** was almost completely converted into **5α**, meanwhile there was a trace amount of compound **4** detected by HPLC. The ammonium salt catalyzed this procedure maybe by exposure of oxygen on nitromethyl group. The reason was that if without the octadecyl dimethyl benzyl ammonium chloride, the inversion of the configuration would be unable to happen even stirring for a week.

All the intermediate compounds were fully characterized by ^1H NMR, ^{13}C NMR and mass spectral data. The structural assignments of the 7α- and 7-isomers were determined by ^1H NMR. It had been reported that the equatorial 7β-nitromethyl derivative **1** and **2** showed ^1H NMR signal for C-7 β nitromethyl group ($-CH_2NO_2$) at 4.76 (dd, J = 12.16, 2.60 Hz, 1H), 4.35 (dd, J = 12.36, 8.70 Hz, 1H) [2] and 4.70 (dd, J = 12.38, 4.26 Hz, 1H), 4.37 (dd, J = 12.40, 9.06 Hz, 1H) [1], respectively. Compound **5α** and **5β** showed ^1H NMR signal for C-7 nitromethyl group at 4.38–4.20 (m, 2H) and 4.73 (dd, J = 12.72, 3.72 Hz, 1H), 4.37 (dd, J = 12.51, 7.64 Hz, 1H), respectively.

With the important compound **5α** in hand, 7α-carboxyl derivative from compound **5α** was achieved by modified Henry reaction [4], without purification, followed by methylation of 7α-carboxy group to afford ester **6** with 80% yield, without detecting any C-7β methyl carboxyl diastereomer of compound **6** by ^1H NMR or HPLC analysis. The ester **6** was converted into Eplerenone **8** by a sequence same to that was previously developed for the construction of 9(11)epoxide [10](Scheme 2). The structure assignment of Eplerenone **8** was confirmed by X-ray (Fig. 3).

In conclusion, we succeeded in an introduction of nitromethyl group at C-7 from commercial available 11α-hydroxy canrenone **4** and a stereochemical conversion of 7β-nitromethyl group into 7α in one step with 90% yield and 96% *de*. An efficient route for the synthesis of Eplerenone **8** was established with easy operation, five steps and 55% total yield and without any expensive or toxic reagent in use Fig. 4.

Acknowledgement

This work was supported by the National Science & Technology Major Project "Key New Drug Creation and Manufacturing Program", China (No. 2009ZX09102-026).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.steroids.2012.04.017.

References

[1] Pearlman BA, Padilla AG, Havens JL, Mackey SS, Wu H. Process to prepare eplerenone and its intermediates from delta 9-canrenone and other pregnanes. USA: Pharmacia & Upjohn Company; 2003 (p. 429).

[2] Nickisch K, Laurent H, Wiechert R. Stereoselective synthesis of 6β,7β -methylene-3-oxo-17α -pregn-4-ene-21,17-carbolactone. Tetrahedron Lett 1981;22:3833–4.

[3] Shapiro EL, Page G, Weber L, Gentles MJ, McPhail AT, Onan KD. Synthesis of 6β,7β-nitromethylene steroids. Tetrahedron Lett 1977;18:3553–6.

[4] Matt C, Wagner A, Mioskowski C. Novel transformation of primary nitroalkanes and primary alkyl bromides to the corresponding carboxylic acids. J Org Chem 1997;62:234–5.

[5] Xu X, Furukawa T, Okino T, Miyabe H, Takemoto Y. Bifunctional-thiourea-catalyzed diastereo- and enantioselective aza-Henry reaction. Chem Eur J 2006;12:466–76.

[6] Trost BM, Yeh VSC. A dinuclear Zn catalyst for the asymmetric nitroaldol (Henry) reaction. Angew Chem Int Ed 2002;41:861–3.

[7] Rabasseda X, Silvestre J, Castaner J. Eplerenone: antihypertensive treatment of heart failure aldosterone antagonist. Drugs Future 1999;24:488–501.

[8] Grob J, Boillaz M, Schmidlin J, Wehrli H, Wieland P, Fuhrer H, et al. Steroidal, aldosterone antagonists. Increased selectivity of 9 α,11-epoxy derivatives. Helv Chim Acta 1997;80:566–85.

[9] Ng JS, Wang PT, Baez JA, Liu C, Anderson DK, Lawson JP, et al. Preparation of 7alpha -carboxyl-9,11-epoxy steroids and intermediates useful therein and a general process for the epoxidation of olefinic double bonds. Application: WO WO. USA: G.D. Searle and Co.; 1997 (p. 271).

[10] Pearlman BA, Padilla AG, Hach JT, Havens JL, Pillai MD. A new approach to the furan degradation problem involving ozonolysis of the trans-enedione and its use in a cost-effective synthesis of eplerenone. Org Lett 2006;8:2111–3.

[11] Wuts PGM, Duda N. Stereoselective alkylation of 7-hydroxy-DHEA derivatives. Synlett 2007:2185–8.

[12] Wuts PGM, Anderson AM, Ashford SW, Goble MP, White MJ, Beck D, et al. A chemobiological synthesis of eplerenone. Synlett 2008:418–22.

[13] Zhang B, Chen H, Feng H, Li Y. Stereoselective construction of a steroid 5[alpha],7[alpha]-oxymethylene derivative and its use in the synthesis of eplerenone. Steroids 2011;76:56–9.

[14] Ng JS, P T, Wang B, Baez J A, Liu C, Vernon Hills I. Processes for preparation of 9,11-epoxy steroids and their intermediates useful therein. G.D. Searle & Co; 2001.

[15] Bernal P, Fernández R, Lassaletta JM. Organocatalytic asymmetric cyanosilylation of nitroalkenes. Chem Eur J 2010;16:7714–8.

[16] Tsogoeva SB. Recent advances in asymmetric organocatalytic 1,4-conjugate additions. Eur J Org Chem 2007;2007:1701–16.

[17] Corey EJ, Zhang F-Y. Enantioselective Michael addition of nitromethane to α, β-enones catalyzed by chiral quaternary ammonium salts. A simple synthesis of (R)-baclofen. Org Lett 2000;2:4257–9.

[18] Dolling UH, Davis P, Grabowski EJJ. Efficient catalytic asymmetric alkylations. 1. Enantioselective synthesis of (+)-indacrinone via chiral phase-transfer catalysis. J Am Chem Soc 1984;106:446–7.