A Nonclassical Stereoselective Semi-Synthesis of Drospirenone via Cross-Metathesis Reaction

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Abstract: A new synthetic approach for the construction of the spirolactone moiety of the progestin drospirenone is presented. A highly efficient cross-metathesis reaction catalyzed by Grubbs–Hoveyda second-generation catalyst (6 mol%) is employed as the key step for the introduction of the ester moiety on to the vinyl group at C17. No protecting groups are required and harmful heavy-metal-based oxidants are not used and this means that this route constitutes a valuable synthetic alternative to existing approaches.

Key words: cross-metathesis, drospirenone, stereoselection, steroids, synthesis

The ready availability of potent agents against human hypertension is of high clinical and public health importance. In this field, an extensive project addressing the discovery of new aldosterone antagonists uncovered the remarkable activity of drospirenone (ZK 30595, 6β,7β,15β,16β-dimethylene-3-oxo-17α-pregn-4-ene-21,17-carbolactone, 1, Figure 1).1 Drospirenone (1) is a spirolactone analogue which exhibits both antimineralocorticoid and antiandrogenic activity very similar to that of the natural hormone progesterone. It is used as an oral contraceptive in combination with ethinylestradiol because of its positive effect in preventing or reducing the change in blood pressure, body weight, and low-density lipoprotein levels that are generally caused by the use of conventional oral contraceptives. Because of its characteristics, drospirenone has found good applications in menopausal HRT (hormone replacement therapy).

To date, numerous synthetic approaches to 1 have been reported with the main focus on the construction of the key 21,17-spirolactone structure.1,2 However, most of them require the use of harmful heavy-metal-based oxidants for the 17-(3-hydroxypropyl) chain (Figure 1).

Among them, chromic acid,3a pyridinium dichromate,3b and ruthenium(III) chloride/sodium bromate3c have found widespread application even in large scale chemistry. However, the concomitant pronounced formation of byproducts as well as large volumes of heavy-metal-containing waste calls for the development of milder synthetic approaches.4 In this direction, the use of inorganic and organic hypochlorites and catalytic amounts of 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO)4cd constitute a valuable alternative.

In the present, study we wish to communicate an unprecedented mild and direct approach for the synthesis of drospirenone (1) starting from 3β,5-dihydroxy-6β,7β,15β,16β-dimethylene-5β-androst-17-one (2).

Scheme 1 Stereosepecific vinylation of 2 via addition of vinylmagnesium bromide

The absolute configuration of the new stereocenter at C17 was confirmed to be S also through X-ray diffraction of 3 (Figure 2). For this analysis, single crystals of 3 were obtained by slow evaporation from a solution of cyclohexane–ethyl acetate (20:80).

Then, in order to introduce the ester moiety, we tested the suitability of 3 as a cross-metathesis partner in combination with some ruthenium catalysts 4a–c (Table 1).5 For this purpose an excess of methyl acrylate (5 equiv) was

Figure 1 Key oxidative step in the synthesis of drospirenone

ZK 30595  (1)
treated with 3 in a degassed solution (CH$_2$Cl$_2$) of 4 (12 mol%).

After 24 hours at reflux, the first-generation Grubbs’ catalyst 4a failed to provide 5, with the recovering of unreacted 3 (80%). In contrast, the second-generation catalyst 4b promoted the cross metathesis in good yield (55%). The highest yield (82%) was obtained in a shorter reaction time (3 h) with the Grubbs–Hoveyda second-generation catalyst 4c (12 mol%), which is known to be very efficient in catalyzing cross-metathesis reactions involving challenging electron-deficient C=C bonds.\textsuperscript{7} Attempts to improve practical aspects of the process were performed by lowering the catalyst loading to 6 mol%. Interestingly, under optimal operational conditions, 5 was isolated in 80% yield (E/Z > 20:1, Table 1, entry 4). Moreover, no preventive protection of the hydroxy groups was necessary for the cross-metathesis reaction.

The catalyst 4c can be also recovered from flash chromatography of the reaction crude and reused (loading 6 mol%) in the model cross-metathesis reaction. Under these conditions, 5 was isolated in moderate yield (53%, Table 1, entry 5).

The ring-closing step to the spirolactone fragment is known to be crucial for the overall success of the synthesis. As a matter of fact, partial epimerization of the C17 carbolactone stereocenter is frequently observed during oxidative ring-closing procedures.\textsuperscript{8} A partial solution to this issue is described in the present synthetic approach. In fact, the ring-closing process can be carried out also in one-pot manner by performing the hydrogenation under higher pressure of hydrogen (8 bar). Here, spirolactone 6 was directly isolated in fairly good yield (60%) after flash chromatographic purification [Scheme 2 (a)]. In contrast, lower pressures of hydrogen (i.e., 1 bar) led to exclusive reduction of the C=C bond in quantitative manner.

Finally, with the synthesis of the C17 lactone already accomplished, the chemoselective oxidation–dehydration of ring A can be performed under mild conditions; a particular concern was to avoid hazardous transition-metal-based oxidants.

In particular, the selective oxidation of C3 by treatment of 6 with two equivalents of Dess–Martin periodinane (CH$_2$Cl$_2$, r.t.) followed by acidic dehydration (PTSA 40 mol%, THF) afforded the desired drospirenone (1) in 60% yield (two steps), without detectable concomitant epimerization of the C17 position [Scheme 2 (b)].

Table 1  Screening of Ruthenium Catalysts in the Cross-Metathesis Reaction of 3 and Methyl Acrylate$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol%)</th>
<th>Time (h)</th>
<th>Yield$^b$ (%) of 5</th>
<th>Recovered 3$^c$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4a (12)</td>
<td>24</td>
<td>0</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>4b (12)</td>
<td>24</td>
<td>55</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>4c (12)</td>
<td>3</td>
<td>82</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>4c (6)</td>
<td>3</td>
<td>80</td>
<td>9</td>
</tr>
<tr>
<td>5$^c$</td>
<td>4c (6)</td>
<td>3</td>
<td>53</td>
<td>20</td>
</tr>
</tbody>
</table>

$^a$ All the reactions were carried out under an inert atmosphere in anhyd CH$_2$Cl$_2$. An excess (5 equiv) of acrylate was employed.

$^b$ After flash chromatography.

$^c$ Recycled catalyst 4c was used.
Considering chemical and environmental aspects, the present semi-synthetic approach can be considered a competitor to known synthetic strategies. In fact, highest overall yield, in comparison with well-established protocols \(^1\) was obtained (25% vs. 16%) and the replacement of hazardous pyridinium dichromate with Dess–Martin periodinane was demonstrated. The yield, in comparison with well-established protocols \(^3\) was obtained (25% vs. 16%) and the replacement of hazardous pyridinium dichromate with Dess–Martin periodinane was demonstrated. Considering chemical and environmental aspects, the present semi-synthetic approach can be considered a competitor to known synthetic strategies. In fact, highest overall yield, in comparison with well-established protocols \(^1\) was obtained (25% vs. 16%) and the replacement of hazardous pyridinium dichromate with Dess–Martin periodinane was demonstrated. Considering chemical and environmental aspects, the present semi-synthetic approach can be considered a competitor to known synthetic strategies. In fact, highest overall yield, in comparison with well-established protocols \(^1\) was obtained (25% vs. 16%) and the replacement of hazardous pyridinium dichromate with Dess–Martin periodinane was demonstrated.

In conclusion, in this communication a new mild and efficient semi-synthesis of drospirenone is presented. No protecting groups are required and this dramatically shortens the synthetic sequence making it suitable even for large-scale productions.

\(^{1}\)H NMR spectra were recorded by means of Varian Gemini-200 (200 MHz) or Varian INOVA-300 (300 MHz) spectrometers with TMS as reference. \(^{13}\)C NMR spectra were recorded on a Varian Gemini-200 (50 MHz) or Varian INOVA-300 (75 MHz) spectrometers with complete proton decoupling with the solvent as the internal standard (CDCl\(_3\); \(\delta = 77.0\)). LC-ESI MS were obtained with Agilent Technologies MSD1100 single-quadrupole mass spectrometer.

**Scheme 2**

(a) Reductive spirolactonization of 5; (b) direct oxidation/dehydration in presence of Dess–Martin periodinane.

**Methyl (E)-[3\(^{\beta}\),5\(^{\beta}\),17\(^{\beta}\)-Trihydroxy-6\(^{\beta}\),7\(^{\beta}\),15\(^{\beta}\),16\(^{\beta}\)-dimethylene-5\(^{\beta}\)-androst-17\(^{\alpha}\)-yl]propenoate (5)**

Allyl alcohol derivative 3 (358 mg, 1.0 mol) was dissolved in degassed CH\(_2\)Cl\(_2\) (10 mL, freezing pump), and methyl acrylate (450 \(\mu\)L, 5.0 mol) was added. The mixture was stirred for 5 min then Grubbs–Hoveyda II catalyst 4c (36 mg, 0.6 mol%) was added in one portion. The mixture was refluxed for 3 h and the volatiles eliminated under reduced pressure. The crude product was purified by flash chromatography to give the product as a white powder; yield: 80%; mp 118–119 °C; \(R_f = 0.3\) (cyclohexane–EtOAc–CH\(_2\)Cl\(_2\), 70:20:10). \(\delta_{\text{H}}^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta = 7.13\) (J = 15.6 Hz, 1 H), 6.12 (d, J = 15.6 Hz, 1 H), 3.42 (s, 1 H), 3.35 (br s, 1 H), 2.71 (br s, 1 H), 2.40 (dd, J = 3.0, 15.0 Hz, 1 H), 1.52–1.59 (m, 2 H), 1.05–1.41 (m, 13 H), 0.95 (s, 3 H), 0.84 (s, 3 H), 0.76–0.94 (m, 1 H), 0.60–0.68 (m, 1 H), 0.38–0.46 (m, 1 H).

**3\(^{\beta}\),5\(^{\beta}\)-Dihydroxy-6\(^{\beta}\),7\(^{\beta}\),15\(^{\beta}\),16\(^{\beta}\)-Dimethylene-5\(^{\beta}\)-androstan-17\(^{\alpha}\)-yl]propenoate (5)**

\(\delta_{\text{H}}^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta = 176.3, 152.4, 118.1, 83.3, 74.8, 67.1, 52.7, 51.7, 44.7, 43.2, 43.0, 40.4, 37.4, 34.2, 27.7, 26.8, 25.3, 24.7, 21.7, 19.0, 18.8, 16.9, 15.2, 11.7, 8.5. LC-MS: \(m/z = 439\) (M + Na\(^+\)). Anal. Calcd for C\(_{25}\)H\(_{34}\)O\(_3\): C, 74.58; H, 9.58. Found: C, 77.12; H, 9.58.

**6\(^{\beta}\),7\(^{\beta}\),15\(^{\beta}\),16\(^{\beta}\)-Dimethylene-5\(^{\beta}\),17\(^{\alpha}\)-pregn-20-ene-3\(^{\beta}\),5,17-triol (3)**

3\(^{\beta}\),5\(^{\beta}\)-Dihydroxy-6\(^{\beta}\),7\(^{\beta}\),15\(^{\beta}\),16\(^{\beta}\)-dimethylene-5\(^{\beta}\)-androst-17-one \((2, 1.5 g, 4.6 mmol) was dissolved in anhyd THF (40 mL) under N\(_2\). The solution was cooled to 0 °C then 0.7 M vinylmagnesium chloride in THF (35 mL, 25 mmol, 5.6 equiv) was added dropwise. The reaction was allowed to warm to r.t. over 2 h, then quenched with sat. NH\(_4\)Cl (15 mL). The organic solvent was evaporated under reduced pressure and the aqueous layer was extracted with CH\(_2\)Cl\(_2\) (3 × 25 mL). The combined organic phases were dried (Na\(_2\)SO\(_4\)) and the volatiles removed under reduced pressure. Pure 3 was obtained through flash chromatographic purification as a white powder; yield: 88%; mp 158–160 °C; \(R_f = 0.3\) (cyclohexane–EtOAc, 50:50). \(\delta_{\text{H}}^{13}\)C NMR (300 MHz, CDCl\(_3\)): \(\delta = 6.02\) (dd, J = 10.8, 16.8 Hz, 1 H), 5.28 (dd, J = 1.5, 16.8 Hz, 1 H), 5.15 (dd, J = 1.2, 10.8 Hz, 1 H), 4.03 (br s, 1 H), 3.49 (m, 1 H), 2.72 (br s, 1 H), 2.20 (dd, J = 3.3, 12.4 Hz, 1 H), 1.93–1.99 (m, 2 H), 1.80–1.87 (m, 1 H), 1.64–1.76 (m, 1 H), 1.11–1.60 (m, 14 H), 0.91 (s, 3 H), 0.84 (s, 3 H), 0.77–0.88 (m, 1 H), 0.58–0.68 (m, 1 H), 0.37 (q, J = 6.3 Hz, 1 H).

13\(^{\beta}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta = 142.6, 112.1, 83.3, 74.8, 67.1, 52.4, 44.8, 43.0, 42.4, 40.4, 37.7, 34.1, 27.1, 26.8, 25.3, 24.4, 21.7, 19.0, 18.7, 16.6, 15.3, 11.7, 8.3.

**LC-MS:** \(m/z = 581\) (M + Na\(^+\)). Anal. Calcd for C\(_{23}\)H\(_{34}\)O\(_3\): C, 77.05; H, 9.56. Found: C, 77.12; H, 9.58.

**Drospirenone (6\(^{\beta}\),7\(^{\beta}\),15\(^{\beta}\),16\(^{\beta}\)-Dimethylene-3-oxo-17\(^{\alpha}\)-pregn-4-ene-21,17-carbolactone, 1)**

In a flamed two-necked round-bottom flask were added in sequence: anhyd CH\(_2\)Cl\(_2\) (10 mL), 6 (160 mg, 0.42 mol), and Dess–Martin reagent (363 mg, 0.83 mmol). The mixture was stirred at r.t. overnight when the reaction was judged complete by TLC. H\(_2\)O (10 mL) was added and after stirring for 15 min, the insoluble white residue was removed by filtration over Celite. The two phases were separated and the aqueous layer extracted with CH\(_2\)Cl\(_2\) (3 × 10 mL).
The combined organic phases were combined, dried (Na₂SO₄), and concentrated under vacuum. The crude was then dissolved in reagent grade THF (5 mL) and PTSA (10 mg, 40 mol%) was added. After stirring at r.t. for 1 h, H₂O (10 mL) was added and the THF evaporated under reduced pressure. After usual workup of the remaining aqueous layer (CH₂Cl₂, brine, Na₂SO₄), analytically pure drospirenone was obtained by flash chromatography as a white solid; yield: 60% (two steps); mp 200 °C; Rf = 0.3 (cyclohexane–EtOAc, 45:55).

[α]D²⁵ –181 (c 0.5, CHCl₃).

1H NMR (200 MHz, CDCl₃): δ = 6.05 (s, 1 H), 2.39–2.61 (m, 4 H), 1.09 (s, 3 H), 1.00 (s, 3 H), 0.42–0.62 (m, 1 H), 0.82–2.19 (m, 18 H).

13C NMR (75 MHz, CDCl₃): δ = 197.6, 176.4, 171.1, 125.6, 103.8, 95.9, 51.6, 51.5, 41.5, 37.2, 36.9, 34.0, 33.8, 30.5, 29.1, 24.2, 20.7, 19.6, 19.5, 18.8, 18.7, 17.4, 16.5, 9.7.

LC-MS: m/z = 367 (M + H)+, 755 (2 M + Na)+.

Anal. Calcd for C₂₄H₃₀O₃ (366.22): C, 78.65; H, 8.25. Found: C, 78.55; H, 8.16.

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