

Chemoselective reduction for different steroidal α,β -unsaturated ketone into diene by using Luche reagent

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Abstract: The conjugate reduction of α,β -unsaturated carbonyl compounds remains an active area of organic synthesis. Our aim is to control the reducing potential and selectivity of conjugated enone reduction. After much experimentation, the best conditions found for maximum yield with chemo and regioselectivity were to employ 1 molar equiv. of NaBH_4 for each mole of substrate in methanol containing some cerium(III) chloride. Many enones were converted essentially quantitatively to the allylic alcohol at room temperature. Surprisingly, reduction of the enone system in compound **2** (1.0 mmol) with NaBH_4 (1.0 mmol) and cerium chloride (1.0 mmol) in MeOH gave compound **3**, in which the enone system was reduced and the allylic alcohol dehydrated producing the diene system.

Keywords: Regioselective; chemoselective; reduction; Luche reagent; diene; ketone. ©2018 ACG Publications. All right reserved.

1. Introduction

The synthesis of natural products is a subject of considerable interest. One of the most fundamental and useful reactions in organic synthesis is the reduction. During the past decades, sodium borohydride has been known as mild and selective reducing agents. The nature of the cation associated with the tetracoordinated borohydride, as well as the choice of the solvent is important in performing selective reduction step. However, reduction of unsaturated carbonyl compounds with sodium borohydride, is highly solvent dependent and generally does not result in a significant regioselectivity.^{1,2} Therefore, combination of NaBH_4 with Lewis acids^{3,4} such as Luche reduction^{5,6} was used to control the reducing potential and selectivity of NaBH_4 in the 1,2-reduction of conjugated enone system. It is believed that the electrophilic assistance occur by either when the cation act as Lewis acid or when the reaction run in a protic solvent.⁷ It was reported that steroidal enone gave the corresponding equatorial allyl alcohol with a high regioselectivity under complexation control when the reaction carried out by using Luche reagent ($\text{NaBH}_4/\text{CeCl}_3$ in MeOH). The interpretation for this regioselectivity was proposed by considering that these reductions take place mainly under Frontier control, and that the enone LUMO-cation interaction is the predominant one. The lower the LUMO level of enone, according to the strength of the interaction with the cation, the faster is the reduction. Therefore, the regioselectivity depends on the relative magnitude of the carbonyl carbon C-2 and the C-4 double bond carbon in the LUMO of the complexed enone system.⁸

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This reaction has continued to attract synthetic chemists and was reported by Zhang and co-workers that it can be utilized for deoxygenation of α,β -unsaturated acylphenols to obtain 2-allylphenols.⁹ Recently, H.B. Borate found during the course of his research involving the Luche reduction of 2-aryl-4-hydroxycyclopent-2-en-1-ones that selective deoxygenation is taking place wherein protected/unprotected hydroxyl functionality is used to afford the 2-aryl-cyclopent-2-en-1-ones in good yields. It is noteworthy that this result for deoxygenation of hydroxyl functionality under Luche reduction conditions is the first time reported in the literature.¹⁰ This inspired us to study the stereo and chemoselective reduction of our steroidal enone to diene systems using $\text{NaBH}_4/\text{CeCl}_3$. We believe that the enone system could be reduced and the allylic alcohol dehydrated upon presence of basic functional groups such as the polyamine side chain to produce the requested diene system.

In our research group, we synthesized several steroidal polyamine and steroidal diamine dimers that mimic the structure of Squalamine and Retrazine, which possess numerous therapeutic properties such as antiangiogenics and antimicrobial and could be safely administered to cancer patients.¹¹⁻¹⁴ It is known that increasing the polar functionalities is expected to increase the biological activities of these steroidal amine compounds. Therefore, we were interested in regioselective reduction of some carbonyl functionalities into ally alcohol. This subject and our continuous efforts to explore new hydroxylated steroidal amine and dimeric steroidal amine encouraged us to investigate reduction of carbonyl functional groups by the Luche reagent. Herein, we wish to introduce an unexpected method for the reduction of a steroidal enone system into the steroidal diene system. There is no reported literature evidence for this unique reduction until this moment.

2. Experimental

2.1. Chemical material and apparatus

Melting points (mp) were determined on an electrothermal digital melting point apparatus. Materials and reagents were obtained from commercial sources and were used without further purification. The FT-IR spectra were recorded on a JASCO FT-IR spectrophotometer employing a 0.1 mm NaCl solution cell. Both ^1H and ^{13}C NMR spectra were recorded on a Bruker AVANCE 400 MHz spectrometer. The chemical shifts (δ) were reported in ppm relative to TMS used as an internal standard. Mass spectra (MS) were obtained from a LC-MSD-Trap_00125 spectrometer with ESI ion source type. Reactions were monitored by thin layer chromatography (Silica gel 60 F254). Solvents were purified according to the standard. A EuroEA Elemental Analyzer performed elemental analyses.

2.2. Chemistry

2.2.1. Synthesis of **2**

To a solution of **1** (0.33 g, 1.0 mmol) in DCE (10.0 mL), 2.0 mL of glacial AcOH was added, and the mixture was stirred under nitrogen at room temperature for 1 hr. Boc-protected spermidine (0.35 g, 1.0 mmol) was added and stirred under nitrogen at room temperature for 24 hrs. $\text{Na}(\text{OAc})_3\text{BH}$ (0.28 g, 1.3 mmol), then glacial AcOH (0.5 mL) were added and the reaction mixture was stirred under nitrogen for 52 hrs. The reaction was neutralized with 1N NaOH and the product was extracted with CHCl_3 (2x20 mL). The organic layer was washed twice with brine (20 mL), dried over anhydrous Na_2SO_4 , and filtered. The solvent was removed under vacuum to yield a yellow oil, which was washed with ether then evaporation under vacuum, to give yellow solid. The yellow solid was dissolved in CHCl_3 (20 mL) and TFA (2.2 mL, 30 mmol) was added and stirred at r.t until no starting material left. The solvent was removed under vacuum and purified by preparative TLC (5% ammonia solution/ethanol) to furnish **2** (0.17 g, 37%); M.p. 135-137°C. FTIR (KBr), ν_{max} 3439, 2947, 1694, 1476 cm^{-1} . ^1H -NMR (CDCl_3 , 400 MHz) δ : 5.73 (d, 1H, H-4), 3.12 (m, 4H, H-22,23), 3.0 (m, 4H, H-25,26), 2.79 (m, 2H, H-29), 1.26 (s, 3H, H-19), 0.84 (s, 3H, H-18). ^{13}C -NMR (CDCl_3 , 100 MHz) δ : 11.2 (C-18), 16.3 (C-19), 39.3(C-22), 54.0 (C-26), 122.8 (C-4), 173.7 (C-5), 200.9 (C-3). M.wt calcd for $\text{C}_{29}\text{H}_{52}\text{N}_3\text{O}$: 458.4110 g/mol; Found 458.4127. MS (ESI), m/z (relative intensity): 458 (M^+ , 100), 427 (M- CH_2NH_2 , 12), 387 (M- $\text{C}_4\text{H}_8\text{NH}_2$, 4).

2.2.2. Synthesis of **3**

Compound **2** (0.45 g, 1.0 mmol) and cerium chloride (0.25 g, 1.0 mmol) were dissolved in methanol (5.0 mL). Sodium borohydride (38 mg, 1.0 mmol) was added in one portion with stirring for 20 min before the pH was adjusted to neutral with 2N HCl. A vigorous gas evolution occurs, together with a temperature rise (~35 °C). The solution was extracted with chloroform (3x20 mL), and the solvent was dried upon evaporation and purified by column chromatography (30 % EtOAc: 70 % Hexane) to give the product **3** (0.33 g, 75%). Mp: 310-311 (d) °C. FTIR (KBr), ν_{\max} 3364, 3223, 2944, 2869, 1631, 1468 cm^{-1} . $^1\text{H-NMR}$ ($\text{CD}_3\text{OD}:\text{CDCl}_3$, 400 MHz) δ : 5.92 (d, 1H, H-4), 5.74 (s, 1H, H-3), 5.6 (m, 1H, H-6), 3.15 (m, 2H, H-22), 0.99 (s, 3H, H-19), 0.81 (s, 3H, H-18). $^{13}\text{C-NMR}$ ($\text{CD}_3\text{OD}:\text{CDCl}_3$, 100 MHz) δ : 11.2 (C-18), 18.1 (C-19), 36.3.3(C-22), 50.0 (C-26), 122.4 (C-6), 124.4 (C-4), 128.8 (C-3), 14 1.2 (C-5). M.wt calcd for $\text{C}_{29}\text{H}_{52}\text{N}_3$: 442.4161 g/mol; Found 442.4152. MS (ESI), m/z (relative intensity): 442 (M^+ , 35), 371 (M-C₄H₁₀N, 20), 327 (M-C₆H₁₅N₂, 100).

2.2.3. Synthesis of **4**

To a solution of **1** (0.35 g, 1.0 mmol) in DCE (10.0 mL) was added putrescine (0.09 g, 1.0 mmol), sodium triacetoxyborohydride (0.43 g, 2 mmol), and 2.0 mL of glacial AcOH. The mixture was stirred under nitrogen at room temperature for 88 hrs. The reaction was neutralized with 1N NaOH and the product was extracted with CHCl_3 (3x20 mL). The combined organic layer was washed twice with brine (20 mL), dried over anhydrous Na_2SO_4 , and evaporated under vacuum to yield a brown yellow oil, which was purified by column chromatography (5% ammonia solution/ethanol) to furnish **4** (0.22 g, 62%); M.p. 145-147°C. FTIR (KBr), ν_{\max} 3410, 2935, 1675, 1616 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 5.70 (brs, 1H, H-4), 2.60 (m, 4H, H-23, 23'), 2.34 (m, 4H, H-22, 22'), 1.51 (m, 4 H, H-24, 24'), 1.16 (s, 3H, H-19), 0.70 (s, 3H, H-18). $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 11.2 (C-18), 16.3 (C-19), 39.3(C-22), 54.0 (C-26), 122.8 (C-4), 173.7 (C-5), 200.9 (C-3). M.wt calcd for $\text{C}_{48}\text{H}_{77}\text{N}_2\text{O}_2$: 713.5985 g/mol; Found 713.5962. MS (ESI), m/z (relative intensity): 713 (M^+ , 96), 413 (M-C₂₁H₃₁O, 52), 384 (M-C₂₂H₃₄NO, 100).

2.2.4. Synthesis of **5**

The dimer **4** (0.37 g, 0.5 mmol) and cerium chloride (0.125 g, 0.5 mmol) were dissolved in methanol (5.0 mL). Sodium borohydride (19 mg, 0.5 mmol) was added in one portion with stirring. A vigorous gas evolution occurs, together with temperature rise (35 °C). Stirring was continued for 20 mins before pH was adjusted neutrally with 2N HCl. The solution was extracted with chloroform (3x20 mL), and the solvent was dried to give upon evaporation the crude product, which was purified by column chromatography (70% Hexane: 20% EtOAc: 10% EtOH) and give dimer **5** (0.34 g, 92%). m.p. 320-323 °C (d). FTIR (KBr), ν_{\max} 3403, 2940, 2869, 1671, 1446 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 5.70 (brs, 1H, H-4), 5.23 (d, 1H, H-4'), 4.05 (m, 1H, H-3'), 3.06 (m, 4H, H-22, 23), 1.51 (m, 4 H, H-24, 24'), 1.23 (s, 3H, H-19), 0.77 (s, 3H, H-18), $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ : 10.9 (C-18), 16.1 (C-19), 39.3(C-22), 55.8 (C-26), 67.0 (C-3'), 122.7 (C-4'), 123.5 (C-4), 146.3 (C-5'), 173.7 (C-5), 200.9 (C-3). M.wt calcd for $\text{C}_{48}\text{H}_{79}\text{N}_2\text{O}_2$: 715.6141g/mol; Found 715.6134. MS (ESI), m/z (relative intensity): 715 (M^+ , 65), 413 (M-C₂₁H₃₁O, 32), 384 (M-C₂₂H₃₄NO, 100).

2.2.5. Synthesis of **6**

The dimer **5** (0.37 g, 0.5 mmol) and cerium chloride (0.12 g, 0.5 mmol) were dissolved in methanol (4.0 mL). Sodium borohydride (19 mg, 0.5 mmol) was added in one portion with stirring. A vigorous gas evolution occur, together with a temperature raise to (~35 °C). Stirring was continued for 20 mins before pH was adjusted to neutral with 2N HCl. The product was extracted with CHCl_3 (2x20 mL). The organic layer was washed twice with brine (20 mL), dried over anhydrous Na_2SO_4 , and filtered. The solvent was removed under vacuum to yield a yellow oil, which was purified by preparative TLC (5% ammonia solution/ethanol) to furnish **6** (0.26 g, 80%). M.p. 327-330 °C (d). FTIR (KBr), ν_{\max} 3396, 3361, 3014, 2940, 2869, 1628, 1444 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 5.76 (d, 2H, H-4, 4'), 5.44 (m, 2H, H-3, 3'), 5.22 (m, 2H, H-6, 6'), 2.92 (m, 4H, H-22, 22'), 2.60 (m, 4 H, H-23, 23'), 1.02 (s,

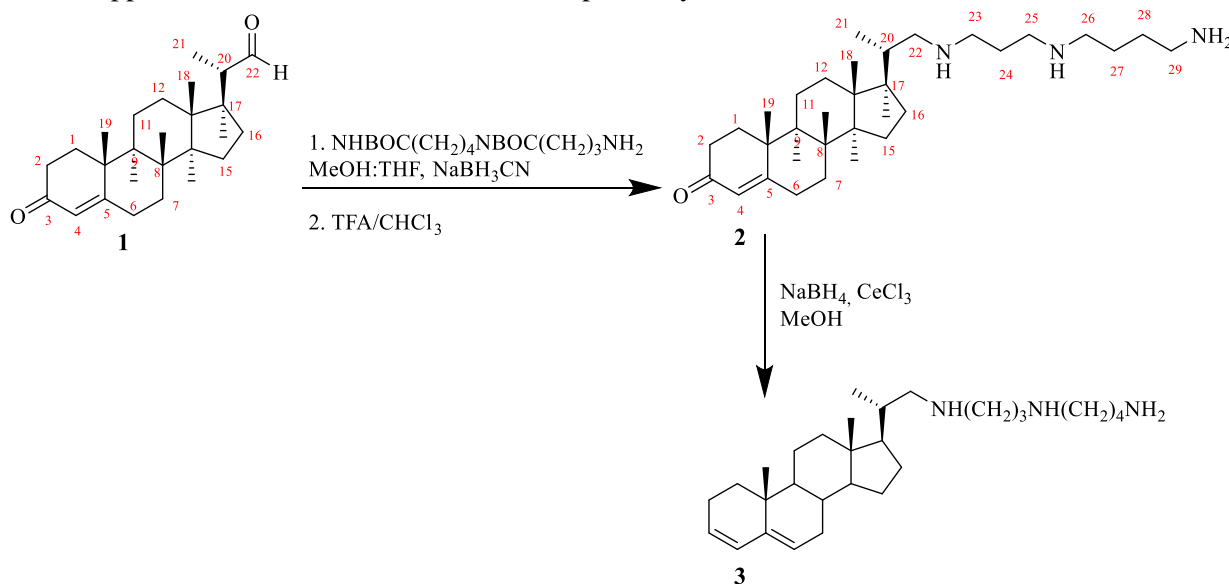
3H, H-19), 0.67 (s, 3H, H-18), ^{13}C -NMR (CDCl_3 , 100 MHz) δ : 11.4 (C-18), 18.1 (C-19), 39.5 (C-22), 53.5 (C-23), 122.4 (C-6), 124.5 (C-4), 128.8 (C-3), 141.3 (C-5). M.wt calcd for $\text{C}_{48}\text{H}_{77}\text{N}_2$: 681.6086 g/mol; Found 681.6084. MS (ESI), m/z (relative intensity): 681 (M^+ , 100), 397 (M-C₂₂H₃₅N, 32), 368 (M-C₂₄H₄₀N, 96).

2.2.6. Synthesis of **8**

To a solution of **7** (0.14 g, 0.5 mmol) in DCE (10.0 mL) was added putrescine (0.045 g, 0.5 mmol), sodium triacetoxyborohydride (0.215 g, 1 mmol), and 2.0 mL of glacial AcOH. The mixture was stirred under nitrogen at room temperature for 88 hrs. The reaction was neutralized with 1N NaOH and the product was extracted with CHCl_3 (3x20 mL). The combined organic layer was washed twice with brine (20 mL), dried over anhydrous Na_2SO_4 , and evaporated under vacuum to yield a brown yellow oil, which was purified by column chromatography (5% ammonia solution/ethanol) to furnish **8** (0.22 g, 22%); M.p. 145-147°C. FTIR (KBr), ν_{max} 3400, 2933, 1685, 1616 cm^{-1} . ^1H -NMR (CDCl_3 , 400 MHz) δ : 6.20 (brs, 2H, H-4, 4'), 2.80 (m, 2H, H-17, 17'), 2.52 (m, 4H, H-20, 20'), 1.54 (m, 4H, H-21, 21'), 1.20 (s, 3H, H-19), 0.93 (s, 3H, H-18). ^{13}C -NMR (CDCl_3 , 100 MHz) δ : 13.8 (C-18), 17.7 (C-19), 47.7 (C-21), 51.1 (C-20), 126.1 (C-4), 160.2 (C-5), 199.2 (C-3). MS (ESI), for $\text{C}_{42}\text{H}_{64}\text{N}_2\text{O}_2$, m/z (relative intensity): 628 (M^+ , 96), 357 (M-C₁₉H₂₇O, 35).

3. Results and Discussion

Reductive amination of the ketobisnoraldhyde **1** (1.0 mmol) with the protected spermidine (1.0 mmol) in DCE using NaBH_3CN as the reducing agent followed by reaction with TFA in CHCl_3 to remove the protecting group on the polyamine gave the polyaminosteroid **2** in 37% yield. The structure of compound **2** was characterized by ^1H -NMR that showed the peak at 5.73 ppm characteristic of the hydrogen on C-4, while the aldehyde peak was replaced by a peak at 3.12 ppm characteristic of the methylene units at C-22 and C-23 (as shown in Scheme 1). The ^{13}C -NMR showed the peak at 200 ppm characteristic of the 3-keto group and the two olefinic peaks at 173, and 122 ppm characteristic of C-5 and C-4, respectively.

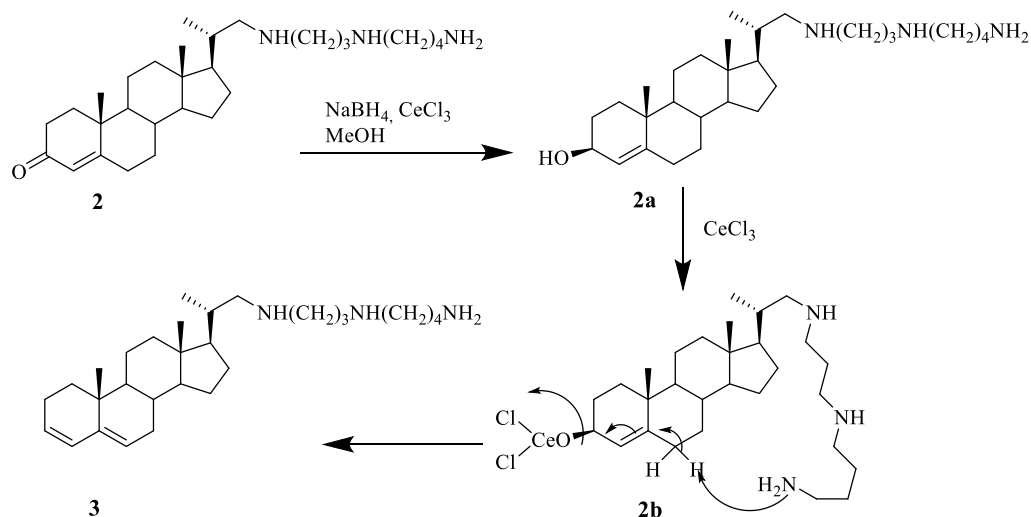


Scheme 1. Synthesis of spermidine steroidal diene **3**

The next target structure was to prepare squalamine analog that has a hydroxyl group on the other end of the steroid (i.e., on the A ring together with the polyamine on the D ring). A Luche reduction applied to effect the 1,2 reduction of steroidal α -enones. Surprisingly, reduction of the

enone system in compound **2** (1.0 mmol) with NaBH₄ (1.0 mmol) and cerium chloride (1.0 mmol) in MeOH (Scheme 1) gave compound **3**, in which the enone system was reduced and the allylic alcohol dehydrated producing the diene system. It is believed that the polyamine side chain plays a role in this transformation, because there is no example in literature that reports the formation of a 1,3-diene from a regular enone system using these (Luche) reagents. ¹H NMR of compound **3** showed a singlet at 5.7 ppm for the hydrogen at C-3, a doublet at 5.9 ppm for hydrogen on C-4 and a multiplet at 5.6 ppm for the hydrogen at C-6.¹⁵

A possible mechanism for the transformation of compound **2** to **3** is shown in Scheme 2.



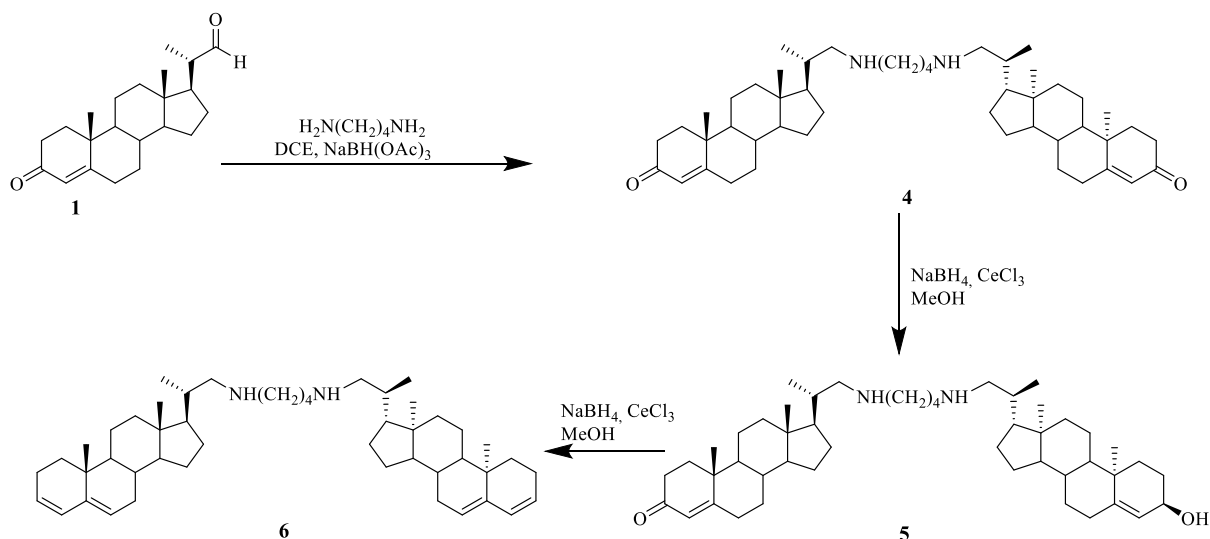
Scheme 2. Possible mechanism for the reduction step

By using the same reductive amination method, the dimer **4** was synthesized in 62% yield. Reductive amination of ketobisnoraldehyde **1** (1.0 mmol) and putrescine (1.0 mmol) in DCE using NaBH(OAc)₃ as a reducing agent (Scheme 3) proved successful. The ¹H-NMR for the dimer **4** showed a doublet at 5.7 ppm characteristic of hydrogen on C-4, and multiplet centered at 2.34 and 2.60 ppm, characteristic of the steroidal methylene unit at C-22, and putrescine methylene unit C-23 respectively. The ¹³C-NMR for the same compound proved that the structure of **4** is symmetrical; showing only 22 peaks, which corresponds to half the compound. Our initial goal was to reduce the carbonyl group at C-3 in order to increase the solubility of the compound in aqueous media, as well as to build a molecule that mimics the structure of squalamine (polyamine and hydroxyl functionality). The reducing agent that was used before (NaBH₄/CeCl₃) gave the diene system. We were interested to learn if the dimer would do the same in the reduction process.

Treatment of the dimer **4** (1.0 mmol) with NaBH₄ (1.0 mmol) and CeCl₃ (1.0 mmol) in MeOH gave compound **5** in 92% yield. Interestingly, only one carbonyl group was reduced and the 3-hydroxyl compound **4** was produced, and not the diene. (Scheme 3). The ¹H-NMR showed the peak at 5.70 ppm characteristic of the hydrogen on C-3 and the peak at 4.0 ppm characteristic of the axial hydrogen on C-3. The ¹³C-NMR gave more information and showed the peaks at 200, 173, 123 ppm, are characteristic for C-3, C-5 and C-4, respectively. The other peaks at 67, 146 and 123 ppm, are characteristic for C-3', C-5' and C-4' respectively. It was suggested that one equivalent of NaBH₄/CeCl₃ reduce only one side of the enone system because the steroids might stack on top of each other.

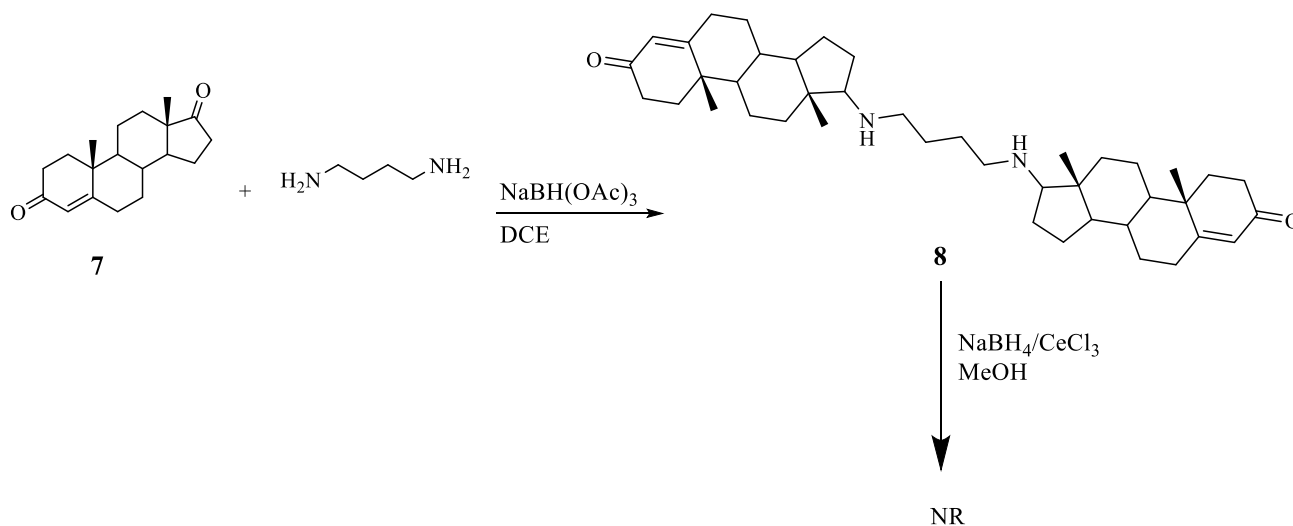
In order to make the explanation more clear, the second equivalent of NaBH₄/CeCl₃ was used to reduce compound **5** and the result was the formation of the diene **6** in 80% yield. One possible explanation is that the CeCl₃ complexes to the hydroxyl group at C-3 and dehydration occurs in the same way that was explained as on Scheme 2 that give the diene on one side. The molecule subsequently changed its geometry and the other carbonyl group was now accessible to the reducing agent, thus the same thing that occurred on the first side could happen on the opposite side (i.e. reduction of the enone to allylic alcohol then dehydration to give the diene).

The $^1\text{H-NMR}$ for the diene **6** showed peaks at 5.76, 5.44, and 5.22 ppm characteristic of the hydrogen on C-4, C-3 and C-6, respectively. The $^{13}\text{C-NMR}$ showed the peaks at 141, 128, 124, and 122 ppm characteristic of C-5, C-3, C-4, and C-6, respectively, in addition to the peaks at 56, and 53 ppm of the C-22, and C-23 that are next to the nitrogen.



Scheme 3. Synthesis of putrescine steroidal diene dimer

In our attempts to prove the importance of the amine functionality role in the dehydration step, we tried the same reduction conditions on different α,β -unsaturated ketones, but all what we got was the allyl alcohol products. One of the readily available diketone we used was 4-Androsten-3,17-dione **7**. Therefore, we decided to synthesize the diamine dimer **8** then reduced it to the diene as in Scheme 4. Attempts to reduce the dimer **8** directly with 2 equiv of $\text{NaBH}_4/\text{CeCl}_3$ but unfortunately, no reduction observed by TLC and NMR. We believe that the reason is the rigidity of the dimer **8**, where the amine is not accessible to act as a base and do the dehydration step. The reduction of these types of dimers are currently undergoing further investigations.



Scheme 4. Attempts for the synthesis of putrescine steroidal dimer **8**

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