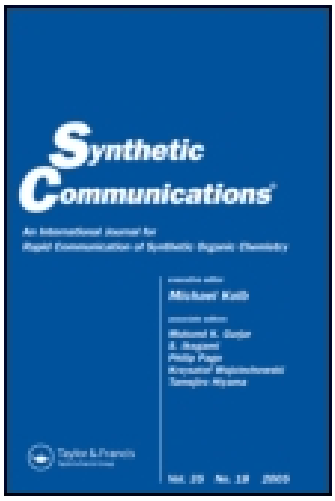

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New, Scalable Route for the Synthesis of a trans-Fused Hexahydro-1H-phenanthren-2-one from a Conjugated Tetrahydro-3H-phenanthren-2-one

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ABSTRACT

A three-step, readily scalable route for the conversion of a ring-conjugated tetrahydro-3H-phenanthren-2-one to a trans-fused hexahydro-1H-phenanthren-2-one is described. The key step is the hydrogenation of a double bond using a nearby ketal moiety to assist in the stereoselective delivery of the hydrogen.

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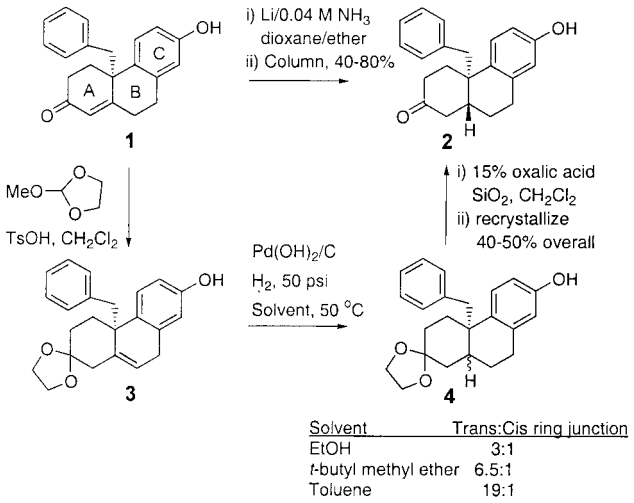
INTRODUCTION

In conjunction with our recently reported development of non-steroidal, selective glucocorticoid receptor modulators,[1] we needed an efficient process for the conjugate reduction of the double bond of the enone system in **1** to the trans-fused A-B ring system in **2**. On a modest scale, this was accomplished by a classical dissolving metal reduction with lithium in ammonia.[2] However, difficulties encountered on the scale-up of this reaction included the need for high dilution conditions to obtain adequate yields of the product and the need for column chromatography to provide pure **2** for further elaboration. Experimentation with several, alternate conditions for the direct stereoselective reduction of the steroid-mimetic **1** to **2** including the use of sodium and calcium in dissolving metal reductions, direct hydrogenation,[3] or phase-transfer hydrogenation[4] did not prove fruitful for the large-scale synthesis of this system. We, therefore, investigated an alternate route for this transformation (Sch. 1).

RESULTS AND DISCUSSION

Formation of the C-2 ketal of **1** with concomitant migration of the double bond from the A to the B-ring afforded **3**. Purification was



Scheme 1.

accomplished simply by stirring an ethyl acetate solution of **3** with activated carbon (Darco®).

In steroids that contain C5-C6 unsaturation in their B-ring, similar to **3**, it is known that catalytic hydrogenation of this C5-C6 B-ring double bond results in good trans-selectivity of an angular substituted A-B ring system.[5] However, when a C5-C6 B-ring double bond is combined with a ketal in the same proximity in the A-ring as in **3**, these moieties can be used as a protecting group for the enone system, while catalytic hydrogenation occurs elsewhere on the molecule.[6] Therefore, the reduction of **3** to **4** required relatively vigorous conditions. Using activated palladium hydroxide on carbon under a 50-psi hydrogen atmosphere at 50°C, **3** was converted cleanly to **4** with interesting solvent effects on the *trans*:*cis* stereoselectivity (Sch. 1).[7] Presumably, the pseudo-axial oxygen of the ketal moiety coordinates the palladium to assist in the beta face addition of hydrogen to **3**. This ketal oxygen–palladium coordination becomes more important for the selectivity of the reduction as the ability of the solvent to coordinate to palladium is decreased. When toluene was used as a ''non-coordinating'' solvent under the aforementioned reduction conditions, **4** was isolated as a 19:1 mixture of *trans*:*cis* ring junction isomers. This highly enriched mixture could be taken to the ketal hydrolysis step of the synthetic sequence without further purification.

Hydrolysis of the ketal was accomplished on acidic silica gel in dichloromethane.[8] After a single recrystallization, **2** was isolated as a single diastereomer,[9] in 40–50% overall yields.

CONCLUSION

In summary, a stereoselective, readily scalable route for the conversion of **1** to **2** has been developed. This route relies on a nearby ketal moiety to coordinate the palladium catalyst and deliver the hydrogen to the desired face of the molecule. This process may have wider application for the stereoselective reduction of other steroid-like systems that prove difficult by other methods.

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EXPERIMENTAL

General

All reagents and anhydrous solvents were obtained from commercial sources. Activated carbon, Darco® G-60, 100 mesh was obtained from Aldrich. Palladium hydroxide on carbon was activated by first suspending the catalyst in acetone and decanting off the solvent to a minimum volume. This process was repeated. The palladium hydroxide on carbon was then suspended in toluene and the toluene was then decanted leaving a minimum of solvent. Again, this process was repeated. The palladium hydroxide on carbon catalyst-toluene slurry was used directly in the subsequent reduction. ^{1}H NMR spectra were measured on Varian XL-400 spectrometers using residual NMR solvent as reference. Mass spectra determinations were performed by the Exploratory Medicinal Sciences Department of Pfizer Global Research and Development at Groton, CT. Thin layer chromatography was performed with EM separation technology silica gel F_{254}. Silica gel chromatography was carried out with E. Merck silica gel (230–400 mesh). Large-scale hydrogenations were carried out in a 2 gallon stainless steel Parr reactor equipped with motorized stirrer, gas inlet valves, block heater and 200 psi pressure gauge.

4a(*S*)-Benzyl-7-hydroxy-3,4,4a,9-tetrahydro-1H-phenanthren-2-one, ethylene ketal (3): To a stirring solution of 48.2 g (0.158 mol) of 4a(*S*)-benzy1-7-hydroxy-4,4a,9,10-tetrahydro-3H-phenanthren-2-one (**1**) in CH_2C1_2 at room temperature under N_2 atmosphere was added 3 g (0.15 mol) of *p*-toluenesulfonic acid. The resultant solution was cooled to 0°C and 3.5 mL (0.063 mol) ethylene glycol was added. To this solution, 22.6 mL (0.237 mol) 2-methoxy-l,3-dioxolane was added dropwise. The resultant solution was stirred at 0°C for 2 h. An additional 5 mL of 2-methoxy-1,3-dioxolane was added and the solution was stirred at 0°C for an additional 1.5 h. One L of sat. $NaHCO_3$ solution was added, the resultant mixture was stirred for 15 min, then the mixture was poured into a 4 L separatory funnel containing CH_2Cl_2 (500 mL) and H_2O (500 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (4X). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to give a dark gum. This residue was dissolved in 250 mL of hot toluene. To this solution was added 7 g of activated carbon and 19 g of solid $KHCO_3$. The resultant mixture was stirred at room temperature overnight, then filtered over a pad of diatomaceous earth and concentrated to give 51 g of 3 as an orange-red solid. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 1.82–1.89 (m, 2H), 2.06–2.17 (m, 2H),

2.32–2.38 (m, 2H), 2.7 (d, 1H, $J = 13$), 2.79–2.85 (m, 2H), 3.20 (d, 1H, J = 13), 3.3 (d, 1H, J = 13), 3.9 (m, 4H), 4.77 (s, 1H), 4.9 (dd, 1H, $J = 4.77$), 6.2 (s, 1H), 6.54 (d, 2H, $J = 7.27$), 6.71 (m, 1H), 7.0 (m, 2H), 7.03 (m, 1H), 7.25 (d, 1H, $J = 8.51$); MS m/z 349 (M + H).

4a(*S*)-Benzyl-7-hydroxy-3,4,4a,9,10,10a(*R*)-hexahydro-1H-phenanthren-2-one,ethylene ketal(4): A Parr apparatus was charged with 89 g of 3 in 50 mL toluene, 27 g of activated $Pd(OH)_2/C$ (see general experimental), 18 g of solid $KHCO_3$ and 2.5 L of toluene. The reaction mixture was sealed, heated to 50°C, pressurized to 50 psi H_2 and stirred for 2 days. The reaction mixture was cooled and filtered over diatomaceous earth with toluene. The mother liquor was subjected to the aforementioned conditions of Pd catalyst and $KHCO_3$, heat, hydrogen pressure, and time for two additional cycles to ensure complete reduction. After the final cycle, the resultant solution was concentrated to give 60 g of 4 as a light yellow gum. ^{1}H NMR (400 MHz, CD_3OD) δ 1.35 (m, lH), 1.6–2.1 (m, 8H), 2.59 (d, 1H, $J = 12.8$), 2.9 (m, 3H), 3.94 (m, 4H), 6.09 (d, 1H, $J = 8.51$), 6.19 (m, 2H), 6.54 (m, 3H), 7.03 (m, 3H); MS m/z 351 (M + H).

4a(*S*)-Benzyl-7-hydroxy-3,4,4a,9,10,10a(*R*)-hexahydro-1H-phenanthren-2-one (2): Into a round bottom flask equipped with an overhead stirrer under N_2 atmosphere containing 2.8 L CH_2Cl_2 was added 1.06 kg SiO_2 (70–230 mesh; E. Merck) with stirring. To the stirring slurry was added 106 g of 15% aq. oxalic acid followed by 88.5 g 4 in 150 mL CH_2Cl_2. The mixture was stirred for 2 days at room temperature. The stirring mixture was cooled to 0°C, 21 g solid $NaHCO_3$ was added, and the resultant mixture was allowed to warm to room temperature over approximately 1 h. The reaction mixture was filtered through a 2 L sintered glass funnel containing 500 g of sand, rinsed with 14 L of CH_2Cl_2, and the CH_2Cl_2 solution was concentrated to dryness. The residue was dissolved into boiling EtOAc (1.5 L) and to the boiling, stirring EtOAc solution was added 700 mL hexanes. The reaction was allowed to cool to room temperature with stirring, overnight. The resultant solid was filtered, rinsed with hexanes, and air-dried to give 33.69 of 2 as a white solid (43% overall). ^{1}H NMR (400 MHz, CD_3OD) δ 1.52 (dt, 1H, $J = 4.5$, 13), 1.64–1.71 (m, 1H), 1.90–2.15 (m, 2H), 2.27 (ddd, IH, $J = 2.5$, 3.7, 15), 2.39 (dm, 1H, $J = 15$), 2.48 (ddd, 1H, $J = 2.0$, 6.5, 13), 2.72 (t, 1H, $J = 14$), 2.84 (d, lH, $J = 13$), 2.89–3.01 (m, 3H), 3.22 (d, lH, $J = 13$), 6.17 (d, lH, $J = 8.5$), 6.24 (dd, lH, $J = 2.5$, 8.5), 6.53 (d, 1H, $J = 2.5$), 6.65–6.68 (m, 1H), 7.04–7.13, (m, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 27.9, 33.7, 34.8, 36.0, 37.6, 39.4, 43.6, 44.0, 111.3, 114.6, 125.7, 127.0, 127.9, 130.5,133.4, 136.8, 138.0, 155.1, 212.7: MS m/z 307 $(M + H)^+$. $[\alpha]_D^{20} = -120°$ (c = 0.0104 g/mL, MeOH). Anal. Calcd. for $C_{21}H_{22}O_2$: C, 82.32; H, 7.24; N, 0. Found: C, 82.27; H, 7.61; N, < 0.10.

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