Synthesis of the Wieland-Miescher Ketone: Michael Addition and a Proline-Catalyzed Annulation

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Introduction

The hormone progesterone, a gonadal steroid, is involved in regulation of the reproductive cycle in women. While the existence of this hormone was known since the beginning of the 20th century, it was not isolated nor its structure characterized until 1934. Progesterone, along with other similar gonadal steroids, is ineffective as a pharmacological agent in its natural form due to poor absorption into the bloodstream; however, similar molecules can be synthesized in the laboratory which overcome this problem. There are two main medicinal purposes for progesterone. It can be used as a birth control agent by preventing the release of the egg at particular points in the menstrual cycle and can be implemented as a treatment for deficiency in this hormone, correcting such manifestations as sterility and irregular menstruation.

Penn State may claim a unique historical connection to the economical synthesis of progesterone through Professor of Chemistry Russell E. Marker. According to information found in the Penn State University archives, prior to Marker’s involvement in the production of progesterone, the hormone was prepared from cholesterol and other animal products at a cost of $80/g (in the early 1940s). Marker was able to synthesize progesterone from diosgenin, a natural product isolated from the root of the Mexican plant Cabeza de Negro, thus reducing the cost of the process considerably down to $3/g. As quoted by Djerassi in Progestin in Therapy—Historical Developments, “Marker’s discovery converted progesterone from the status of an expensive rarity to the cheapest of all steroid hormones.”

The success of these investigations into the progesterone synthesis is best stated by Marker himself: “During the year (1944) I produced over 30 kilograms of progesterone... by methods I had developed at Penn State.”

We chose to synthesize the Wieland-Miescher ketone, (S)-8a-methyl-3,4,8,8a-tetrahydro-1,6(2H, 7H)-naphthalenedione, an intermediate in progesterone synthesis. The Wieland-Miescher ketone may serve as starting material for a wide variety of natural product syntheses. The synthesis used in this experiment yields an enantiomerically pure product; it and similar preparation techniques have paved the way for this ketone’s frequent selection as a precursor to the synthesis of biologically relevant molecules in their optically pure state. As many biological compounds naturally occur in only one enantiomeric form, and as changing a chiral center can have drastic, if not lethal, effects, such syntheses are incredibly important in modern chemistry. There are two general ways in which asymmetric syntheses are performed: one incorporates chiral fragments of known stereochemistry, while the other employs chiral catalytic molecules to direct the target stereochemistry.

Because the Wieland-Miescher ketone is so well characterized, it is often used as a testing material for asymmetric syntheses. One asymmetric synthesis recently described is that of taxol, an extremely potent anti-cancer agent. Catalytic asymmetric synthesis is frequently accomplished under the influence of steric hindrance. For example, both noradrenalin and L-amino acids may be synthesized using amalgams and solid catalysts dependent upon stereospecific addition to the less hindered undersides of the molecule.

The first synthetic step is a Michael addition between ketone 1 and dione 2 (Scheme I); the resonance-stabilized enolate of 2 attacks 1 via 1,4-addition to the carbonyl. Subsequent protonation and tautomerization gives prochiral 3.

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Exclusively the $S$ enantiomer of the Wieland-Miescher ketone 4 is produced via a Robinson annulation of 3, in an asymmetric catalysis by L-proline (Scheme II).

One proposed transition state of an L-proline reaction for a similar intermediate is shown in Figure 2. Hajas and Parrish indicate that the proline acts like an enzyme in that it forms specific hydrogen bonds with the intermediate that arrange the substrate in a conformation conducive to formation of 4S.\(^9\) The exact mechanism of this catalysis is still under investigation, but the literature favors this scheme.
Figure 2: L-proline catalyzed transition state for another triketone.

For the modeling part of this project you should try to build the transition state structure shown in Figure 2. There is an atom missing in this structure. Can you find it? Also calculate the energies of the R & S enantiomers of 4. Are the semiempirical equilibrium geometry energies the same. Why or why not?

There are several available variations on the presented procedure for creating 4. DMSO is often used as the solvent for the second step of the reaction although DMF was preferred due to its lower boiling point (DMSO = 189 °C, DMF = 153 °C). Recent reports have also presented a single step synthesis of 4 as shown below.

Figure 3: An alternative one step synthesis of 4

This variation has slightly lower yields than those reported for the two-step process (49 vs. 57%). The main disadvantage in this single step pathway is the limited availability to study the intermediate 3 since it is never isolated and purified. Also, the timeframe for reactions required in the two-step synthesis is a more appropriate fit to the time schedule in the advanced organic laboratory. Another potential pathway to 4 involves the use of aldolase antibody 38C2, the first commercially available catalytic antibody. This scheme produces a higher overall yield and ee of 4 compared to the L-proline catalyzed version run under similar conditions (yield 94% vs. 83%, ee 96% vs. 83%). The major disadvantage with this reaction is the extremely high cost of the antibody and the requirement for cold storage with limited shelf life.

Results and Discussion

The Wieland-Miescher ketone 4 (8a-methyl-3,4,8a-tetrahydro-1,6(2H, 7H)-naphthalenedione) was synthesized in a two-step reaction involving a Michael addition and an L-proline catalyzed Robinson annulation. Intermediate triketone 3 was prepared from a reaction of ketone 1 with dione 2, to produce 1.30 g (83%) of a yellow oil. The Wieland-Miescher ketone 4 was synthesized from triketone 3 under catalysis by L-proline, yielding 0.68 g (58%) of a dark red-brown oil.

The identity of the intermediate 3 was confirmed through 1H NMR and GC-MS analysis. To assist in the assignment of peaks in the 1H NMR of 4 a heteronuclear multiple quantum coherence (HMOC) 2-D experiment was performed. A portion of this data is shown in Figure 4.
The chiral methyl group is visible in the red circle as both the $^1$H and $^{13}$C shifts are quite upfield (1.4 and 23 ppm respectively). The blue colored region is seen as a set of points in the spectra due to the similar $^1$H shifts but significantly differing $^{13}$C shifts. The purple and orange regions can be distinguished based on their $^{13}$C shifts. The orange region will be slightly deshielded by the adjacent carbonyl group compared to the purple region, which is in a fairly aliphatic region. A strong signal for the green protons was not seen in this HMQC data although it may be represented by the small point located directly upfield (at around 1.5 ppm) from the red group. Based on this data confident peak assignments could be made in the $^1$H NMR data.

Silica gel column purification of the final product mixture was found to be ineffective at totally removing all impurities as demonstrated by retained black color in the eluent. Decolorization with Norit™ activated charcoal pellets proved to be ineffective as well. One successful technique for removing impurities was found to be packed column preparatory GC. Since only 10 – 15 mL of sample could be injected for each run, the process was repeated 6 times to collect enough pure product for spectral analysis. Figure 5 shows one of the chromatograms produced by this method.

The large peak on the left represents impurities plus residual ethyl acetate and DMF from the silica gel column eluent that was not removed under the vacuum. All eluent after the arrow was collected into a capillary glass tube. The purified product formed dark orange-red crystals in the tube. Spectral analysis indicated a pure compound and no additional peaks for solvent (DMF) were seen.

To confirm optical purity, polarimetry was performed on the product Wieland-Miescher ketone 4. A positive value $[\alpha]_D^25 +15^\circ$ (in toluene) for specific rotation was obtained in a preliminary experiment, indicating that 4 rotates light in the same direction as the literature predicts ($[\alpha]_D^25 +97^\circ$ in toluene), which verifies that the majority of the product is the S conformer. It is not possible, using the presented data, to prove with certainty that the ketone 4 is optically pure, but the proposed literature mechanism requires asymmetric catalysis. Further
polarimetry experiments with larger amounts (> 20 mg) of pure 4 are required to make a conclusive determination of optical purity.

The thermodynamic equivalence, as calculated by molecular modeling, of 4R and 4S is noteworthy in that a traditional racemic synthesis would produce equal amounts of the enantiomers. Our calculations demonstrate that the enzymatic principles of this synthesis, not the thermodynamic properties of the products, dictate the exclusive synthesis of 4S.

The original procedure for the presented scheme was designed for approximately one mole of starting dione 2. For this investigation the reaction scale needed to be scaled down dramatically. As a result several difficulties in the procedure were encountered and modifications were made. First, the reaction time required for the formation of 3 was found to be significantly longer than one hour as reported for the large-scale version. As a modification the first step was carried out over approximately 48 hours, or until all the solid dione 2 dissolves thus producing a yellow solution of the product. One problem associated with the extended reaction time is the potential for polymerization by ketone 1. This reaction is known to proceed by a free radical pathway and therefore it is proposed that BHT may prevent this polymerization when added in small amounts. Additional studies are required to identify the effectiveness of BHT and to prove that it does not interfere with the reaction as proposed. Further investigations should also be focused on determining a more appropriate solvent for the second step since both DMF and DMSO have high boiling points and therefore are difficult to remove from the final product mixture. Some success was obtained through the use of high-vacuum distillation with a cold trap although traces of the solvent (DMF) were still seen in the 1H NMR spectra.

Experimental

Spectral Measurements: 1H NMR and HMQC (heteronuclear multiple quantum coherence) analysis were performed on a Bruker Biospin (Billerica, MA) Advance 400 NMR (400 MHz) Spectrometer (1H peak assignments indicated by color key, Figure 6). TLC analysis was performed using polyester-backed silica gel plates (IBF-2) obtained from J. T. Baker (Phillipsburg, NJ). Mobile phase gas chromatography was carried out on a Hewlett Packard (Palo Alto, CA) 5890 Series II GC using a 30m x 0.250mm i.d. capillary column with a 25 μm coating of 5% phenyl / 95% methyl silicone which was programmed from 40 to 280 °C at 10°/min. GC-MS was carried out on a Hewlett Packard (Palo Alto, CA) 5972 GC-MS using the same column and temperature program. Preparatory GC was performed using a Varian (Walnut Creek, CA) Model 920 GC with a 5 feet x 2 mm x _ inch i.d. column packed with a 3% coating of OVI and a temperature setting of 205°C. Polarimetry data was collected on a PerkinElmer (Shelton, CT) 531 polarimeter. Equilibrium geometry of 4 was calculated using semi-empirical PM-3 calculations in Mac-Spartan Pro 1.0.2 (Wavefunction Inc., Irvine, CA).

Chemicals: Methyl vinyl ketone (99%), 2-methyl-1,3-cyclohexanedione (97%), hydroquinone (99%), and L-proline (99%) were purchased from Aldrich Chemical Co. (Milwaukee, WI). N,N-dimethyl formamide (99.8%) was purchased from EM Science (Cincinnati, OH). All chemicals were used without further purification.

**Figure 6:** Spectral data key for 3 and 4, respectively.

2-methyl-2-(3-oxobutyl)-1,3-cyclohexanedione, 3: A mixture of 1.3 mL of methyl vinyl ketone (1, 1.05 g, 14.9 mmol), 1.00 g of 2-methyl-1,3-cyclohexanedione (2, 7.93 mmol), and 8.7 mg of hydroquinone, 0.024 mL glacial AcOH, and 2.4 mL H2O was combined in a 20 mL screw-top vial which was flushed with N2 and placed in a 50 °C incubator for 48 hr. The resulting yellow oil was cooled to room temperature and combined with 3 mL sat. aq. NaCl. The water layer was extracted with EtOAc (2 x 10 mL), and the combined organic layers were back extracted with sat. aq. NaCl (2 x 10 mL) and dried over anhyd Na2SO4. The solvent was removed under vacuum to yield 1.30 g (83%) of 3, a pale yellow oil. TLC (3:2 ethyl acetate:hexane): Rf 0.50. MS m/z (% rel. int.): 196 (11, M2), 178 (11, [M-H2O]+), 125 (20, [M-C3H7O]+), 111 (39, [M-C5H9O2]+), 43 (100, [CH3CH2 CH2]+). 1H-NMR (400 MHz, CDCl3): δ 2.5-2.7 (m, 2H, orange H’s), 2.3 (t, 2H, purple H’s), 2.1-2.2 (m, 4H, blue H’s), 2.05 (s, 3H, red H’s), 1.9-2.0 (m, 2H, green H’s), 1.15 (s, 3H, pink H’s).
(S)-(+) -8a-methyl-3,4,8a-tetrahydro-1,6(2H,7H)-naphthalenedione, 4: L-proline (80 mg) was added to the 2-methyl-2-(3-oxobutyl)-1,3-cyclohexanedione (3) isolated in the previous step that had been dissolved in 10 mL of anhyd DMF. The mixture was stirred for 120 hr, and the solvent removed under vacuum. A 4 x 6 cm silica gel (230-400 mesh) column was packed in hexane, eluted with 20 mL of 5:1 hexane:ethyl acetate, then eluted with 3:2 hexane:ethyl acetate. The dark-colored fractions were combined and solvent removed under vacuum. To obtain high-purity product for spectral analysis, 6 x 10 mL samples were purified via preparatory GC. The remaining dark-colored oil was placed under high vacuum for 5 hr to yield 0.68 g (58%) of 4, a dark red-brown oil. MS m/z (% rel. int.): 178 (33, M⁺), 160 (43 [M-H₂O⁺]), 121 (100, [M-C₅H₅⁺]), 79 (90, [M-C₆H₇⁺]). ^1H NMR (400 MHz, CDCl₃): δ 5.8 (s, 1H, pink H’s), 2.6-2.7 (m, 2H, orange H’s), 2.35-2.5 (m, 4H, blue H’s), 2.0-2.1 (m, 2H, purple H’s), 1.6-1.7 (m, 2H, green H’s), 1.4 (s, 3H, red H’s). [D]_25^s +15.0° (toluene). [H](from molecular modeling): 4S and 4R = 50.87 kcal/mol.
Notes, References, and Acknowledgments

14. Reference 13 states that the products are not enantiomerically pure; this is in direct conflict with Reference 5. At this time we have no explanation for this discrepancy.
15. $108.70 / 10 mg for antibody vs. $43.10 / 100 g for L-proline, both from Aldrich.
16. Special thanks to Jason Waldkirch (PSU) for assistance in obtaining polarimetry data.