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Synthesis of a C, D Ring Analog of 17-α-Hydroxyprogesterone

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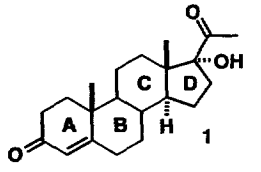
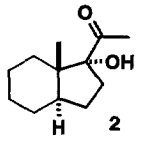
Abstract: The synthesis of an optically active C, D ring analog of the angiostatic steroid 17-α-hydroxyprogesterone was carried out. © 1997 Elsevier Science Ltd.

Angiogenesis is the growth and proliferation of new blood vessels and is important in the growth of solid tumors.[1] Investigations have revealed that heparin, when administered in conjunction with certain, otherwise biologically inactive steroids, exhibited powerful anti-angiogenic (angiostatic) effects. The angiostatic activity was found to be dependent on the source of the heparin.[2] It has been found however, that lower molecular weight fragments of heparin, synthetic heparin analogs, and sulfated cyclodextrins exhibit similar angiostatic activity when administered in conjunction with angiostatic steroids,[1,3] but display none of the undesirable anti-coagulant effects of heparin.

The steroids that were found to exhibit this angiostatic activity exhibited structural similarities in the C and D rings, but had a wide range of features in their A and B rings. It was found that the 17-α-hydroxyl, and the presence of carbons 20 and 21 in the steroid structure were required for activity.[3] Specifically 17-keto steroids were inactive, as were 20-keto steroids lacking the 17-α hydroxyl group. In order to investigate the contributions of the A and B rings to the angiostatic activity, the synthesis of a C, D ring analog of 17-α-hydroxyprogesterone was undertaken.



17-α-Hydroxyprogesterone

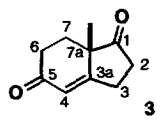


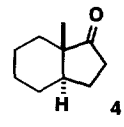
17-α-Hydroxyprogesterone
C, D ring analog

Figure 1.

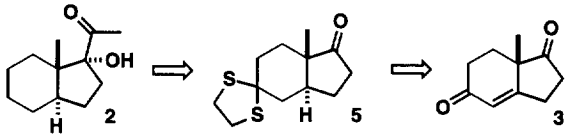
With the optically pure hydrindenedione **3** readily available,[4] it was desired to find a method compatible with the use of this compound as the starting material. Use of **3** to access the target would require solutions to several problems. 1) attachment of the required side chain in a stereocontrolled manner at carbon 1; 2) establishment of the thermodynamically disfavored *trans* ring fusion; and 3) differentiation of the two ketone carbonyls to allow deoxygenation of the enone carbonyl at the 5 position.

For the installation of the side chain at carbon 1, a variety of synthetic methods used in steroid systems were available.[5-11] The precursor for all methods was envisioned as a dithiolane-ketone **(5)** as shown in **Scheme 1**. The dithiolane would be installed early in the sequence to differentiate the two ketone carbonyls, and be retained through the attachment of the side chain to avoid problems that would arise from volatility of the intermediates lacking the dithiolane. Racemic hydrindanone **(4)** is





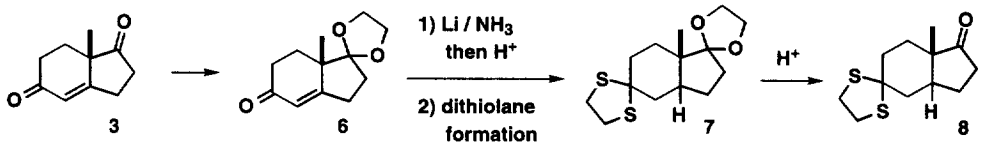
reported to be a volatile oil with a camphor-like odor.[12] The dithiolane should also impart crystallinity in the intermediates. This property was desirable in that the unambiguous confirmation of the *trans* ring fusion would probably require an x-ray analysis of at least one of these intermediates.



Scheme 1.

The generation of the *trans* ring fusion was envisioned as a much more difficult problem than the installation of the side chain. Inspection of the literature revealed that only a few methods were available for the generation of the *trans* ring junction in hydrindanes starting with an enone precursor unsubstituted at the 4 position. A method had been described for the production of the *trans* fused system in the racemic system via dissolving metal reduction of the enone **6**, prepared by selective ketalization of the saturated ketone in **3**.[13]

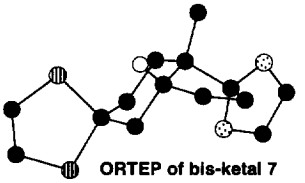
Ene-dione **3** was prepared in optically pure form by a proline catalyzed annulation,[4] then selectively protected and subjected to reduction with lithium in ammonia according to the literature procedure.[13] Manipulation of the protecting groups then led to ketone **8**. **(Scheme 2)** The installation of the side chain at this point could not be accomplished under a variety of conditions that were successful on the D ring of the complete steroid skeleton.[14]



Scheme 2.

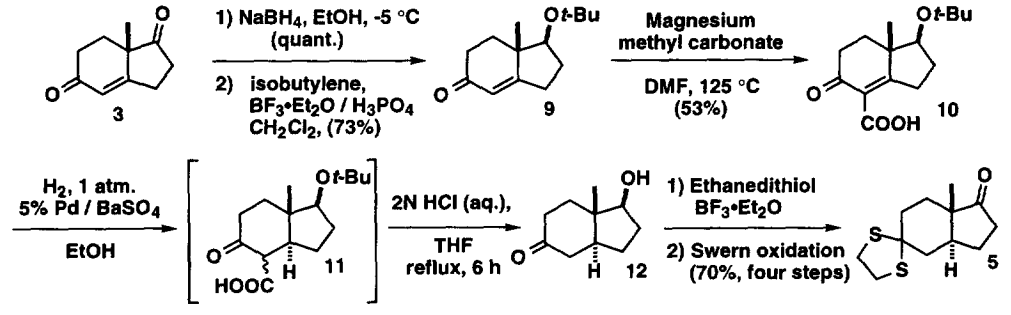
This puzzling result led us to investigate the structure of this ketone (**8**) more carefully. The infrared spectral data reported[13] for the *cis* and *trans* isomers of the saturated ketone obtained from lithium / ammonia reduction of the ketal (**6**) were almost identical, differing from each other by only a few absorptions. The ^1H NMR spectra of the two products were also similar enough to prevent conclusive determination of the ring junction stereochemistry based on comparison of these data alone. In order to compare the material obtained from the lithium / ammonia reduction with the *cis* fused isomer, a small portion of the ketal (**6**) was hydrogenated to the saturated ketone using palladium on carbon in methanol. This procedure was reported to afford the *cis* fused product.[15] The material obtained from this hydrogenation was identical in all respects to the material prepared by the lithium / ammonia reduction of the enone in contrast to the original report.

Soon after the discovery of the identity of the ketones obtained by the two different methods of reduction of the enone, a single crystal x-ray analysis of the bis-ketal (**7**) was completed. The x-ray conclusively demonstrated that the product obtained from both reduction methods was in fact the *cis* ring-fused isomer. A search of the literature indicated that there was never a correction published for this error. Acquisition of the *cis* isomer by dissolving metal reduction of ketal-enone (**6**) is briefly mentioned in a paper by the same authors several years later.[16] It appears that the "*cis*" and "*trans*" compounds for which the authors report analytical data in the earlier paper,[13] are in fact the same materials.


ORTEP of bis-ketal 7

With the discovery of this error, another method for the establishment of the *trans* ring junction was required. A five-step route involving temporary substitution of the 4-position with a carboxyl group, followed by hy-

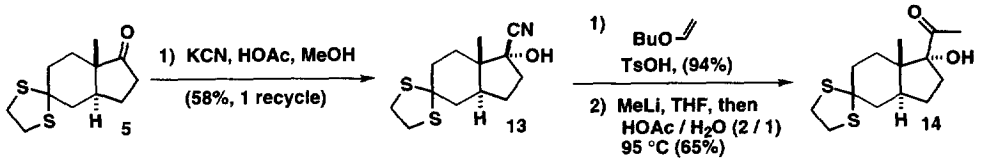
drogenation of this 4-substituted hydrindene was reported to afford the *trans* ring fused product predominantly.[17] (**Scheme 3**) The ene-dione (**3**) was converted into keto-alcohol (**12, Scheme 3**) by a five step protocol in good overall yield.[18] Substitution at the 4 position of the hydrindanone in this case leads to the establishment of the *trans* ring junction during the hydrogenation. After treatment of the ketone (**12**) with ethanedithiol and BF_3•Et_2O, the resulting alcohol was oxidized under Swern conditions[19] to afford ketone **5**. This desired *trans*-ketone was obtained in 70% overall yield for four steps by recrystallization from ethyl acetate / hexane. Single crystal x-ray analysis of ketone **5** confirmed that the *trans*-ring fusion has been established.



Scheme 3.

Treatment of ketone **5** with ten equivalents of KCN and eight equivalents of acetic acid in methanol, followed by recrystallization of the crude product from ethyl acetate / hexane afforded 35% of the desired cyanohydrin (**13**) as large colorless prisms. (**Scheme 4**) The residue obtained from the mother liquors could then be resubmitted to the reaction conditions, and recrystallized to afford an additional 23% of the desired β-cyanohydrin (**13**). Flash column chromatographic purification of the mother liquors afforded more of the desired product, (~10% additional pure product). The high mass balance of these procedures (94% for the one recycle) made this protocol an efficient procedure for the preparation of large quantities of **13**. Single crystal x-ray analysis of this material showed that the *trans* ring junction had been maintained, and that the cyano group is in the desired β-orientation.

Protection of the hydroxyl group of the cyanohydrin was carried out with butyl vinyl ether and catalytic *p*-toluenesulfonic acid in THF in 94% yield.[10] The protected cyanohydrin was then treated with methyl-lithium, and subsequently heated in aqueous acetic acid to afford the desired hydroxy-ketone in 65% yield. Single crystal x-ray analysis of the product confirmed that the methyl ketone side chain was in the desired configuration.

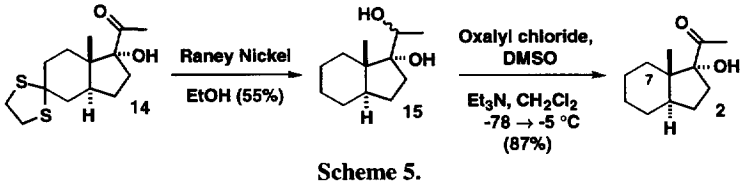


Scheme 4.

Treatment of the hydroxy-ketone (**14**) with freshly prepared Raney nickel[20] in absolute ethanol at ambient temperature rapidly consumed the starting material and afforded two major products by TLC analysis. The two products were isolated and identified as the two diastereomers of the diol (**15**) arising from removal of the dithiolane with concomitant reduction of the ketone carbonyl (**Scheme 5**). Deactivation of the Raney nickel by prior refluxing in acetone, or carrying out the reduction at 0 °C also led to reduction of the ketone at a rate competitive with the desulfurization. Oxidation of the diols (**15**) to the desired hydroxy-ketone (**2**) could

be accomplished under Swern conditions in 87% yield.

One and two-dimensional NMR experiments were carried out to confirm the structure of the product. The angular methyl group appears as a 0.7 Hz doublet in the proton spectrum. This coupling is the result of a long range W coupling with the α proton of the adjacent C-7 methylene. This is in agreement with results obtained by other workers investigating these long range couplings in *trans* fused systems of this type.[21] The two dimensional NMR experiments, in combination with mass spectral and IR data allowed us to confidently assign the structure as shown.



Scheme 5.

Preliminary tests indicate that ketone **2** retains some of the anti-angiogenic activity of 17-α-hydroxyprogesterone when administered in conjunction with β-cyclodextrin tetradecasulfate.[22] The results of this angiostatic testing lends support to our contention that the A and B rings of the angiostatic steroids are not absolutely necessary for their angiostatic activity. In future investigations we would like to prepare analogs containing hydrophobic side chains at the 4 position of the hydrindane skeleton. It is hoped that the resulting increase in hydrophobicity will improve the analogs' angiostatic activity. Several synthetic routes to this analog are being considered.

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