

A SHORT EFFICIENT SYNTHESIS OF 19-NORANDROST-4-ENE-3,17-DIONE¹

Gary F. Cooper* and Albert R. Van Horn
Syntex Research, Institute of Organic Chemistry
Palo Alto, California 94304

Abstract. A three-step conversion of 3 α -H-4 α -(3'-propionic acid)-7 $\alpha\beta$ -methylhexahydro-1,5-indanedione into 19-norandrost-4-ene-3,17-dione is described.

Recent advances in the microbial degradation of the abundant soya sterols sitosterol/campesterol have made 3 α -H-4 α -(3'-propionic acid)-7 $\alpha\beta$ -methylhexahydro-1,5-indanedione (1a), a potentially useful starting material for 19-norsteroid synthesis, readily available². This crystalline diketoacid is an attractive starting material for several reasons: 1) it possesses the natural steroid absolute configuration, 2) it possesses exclusively the trans indane ring fusion which has frequently been difficult to obtain cleanly in total synthesis schemes³, and 3) it possesses the 17-keto function (steroid numbering) useful for future elaboration by nucleophilic addition to give medicinally important 19-norsteroids (e.g., 17 α -ethynyl-19-nortestosterone (2) an orally active progestin). A previous total synthesis, involving the related bicyclic acid 1b, required subsequent deprotection and oxidation at C-17 to give the title compound⁴.

We present here an efficient, three-step conversion of 1a into 19-norandrost-4-ene-3,17-dione (3), a precursor of 2. Condensation of 1a with one equivalent of pivaloyl chloride in the presence of one equivalent of triethylamine in THF at -20°C gave the mixed anhydride 4 which, without isolation or removal of precipitated triethylamine hydrochloride, was cooled to -70°C and treated over 40 minutes with one equivalent of a 1M solution of the Grignard reagent 5a⁵, derived from 5-chloro-2-pentanone ethylene ketal, in THF⁶. After one hour at -70°C the reaction mixture was warmed to -20°C and quenched with H₂O. Removal of the THF in vacuo followed by the addition of methanolic KOH, reflux under N₂ for one hour, and neutralization with glacial acetic acid afforded a mixture of the desired tricyclic enedione 6a⁷, starting material 1a and the ketoketal 7. The latter two products are the result of attack of the Grignard reagent on the pivalic carbonyl of the

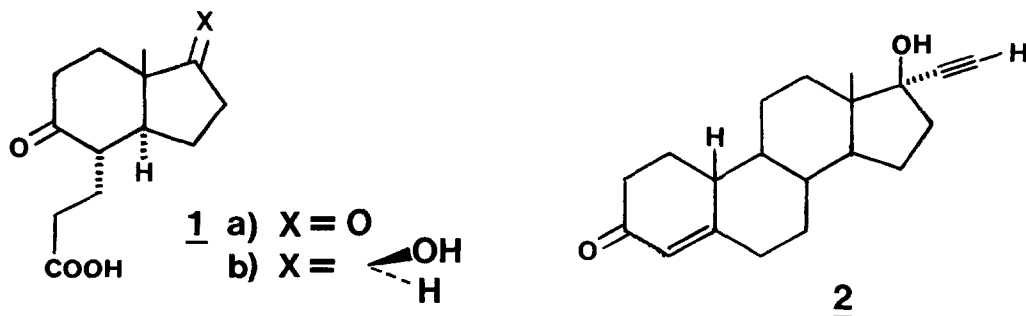
mixed anhydride. After removal of the methanol in vacuo the products were extracted into ether and residual 1a washed out with aqueous sodium carbonate. After drying and concentration pure 6a could be isolated in 80% overall yield by chromatography on silica gel using an ethyl acetate/hexane gradient⁸. This represents a considerable improvement over the previous total synthesis in which bicyclic hydroxy acid 1b was converted to the related tricyclic 6b in 28.7% overall yield via reaction of the acetoxyenollactone 9 (obtained in one step from 1b) with Grignard reagent 5b, base catalyzed cyclization, removal of the ketal function, and benzylation at C-17⁴.

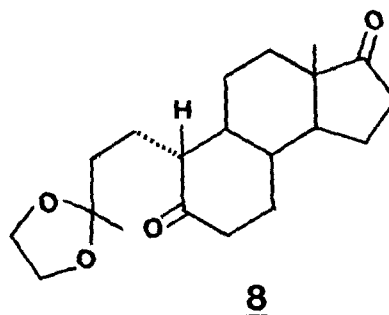
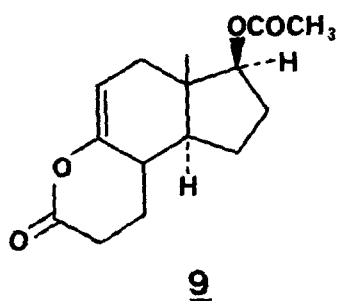
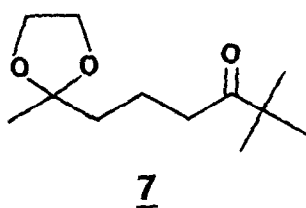
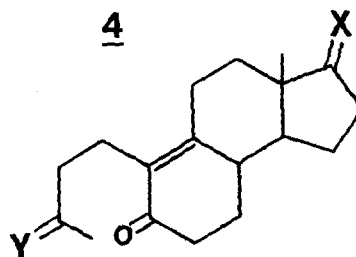
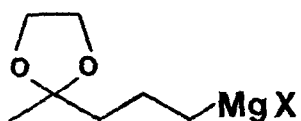
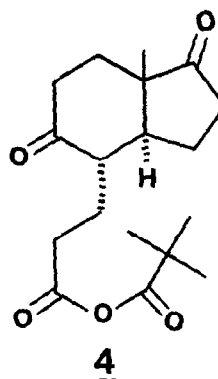
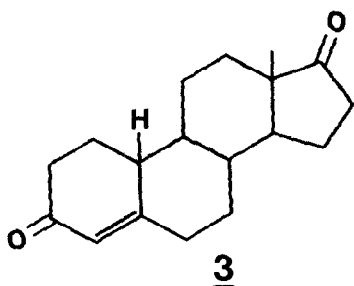
Catalytic hydrogenation of 6a over 5% Pd on C in 10% v/v triethylamine in methanol afforded the dione 8 which, after removal of the catalyst by filtration, was directly deprotected and cyclized to 3 by refluxing in methanolic hydrochloric acid. Addition of water to the cooled solution precipitated crystalline 3 in 64% overall yield from 1a.

The sodium carbonate washes from the workup of 6a were acidified to pH=1, saturated with NaCl, and extracted with methylenechloride. After drying and concentration in vacuo, trituration with hexane afforded recovered 1a in 20.8% crude yield. Recrystallization from isopropylacetate gave pure 1a in 17.7% yield.

Discussion

In agreement with the previous findings of Mukaiyama⁶ for a different system, the reaction of the Grignard reagent 5a with the mixed anhydride 4 is highly regioselective. No by-products resulting from the addition of 5a to either of the ring carbonyl groups on 4 could be detected. The fact that the ratio of attack at the two carbonyl groups of the mixed anhydride moiety is only 80/20 in favor of the desired product is mitigated by the ease of recovery of the valuable chiral fragment 1a. Thus, 3 has been prepared quickly and in good yield without the need for protecting the 17-carbonyl group.





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REFERENCES AND NOTES

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8. Chromatography may be omitted and the by-product 7 carried through to the end. Hexane washing of the crude product removes 7.

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