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Ag(I)-ASSISTED HYDROLYSIS OF MESTRANOL METHANESULFONATE INTO EPIMESTRANOL

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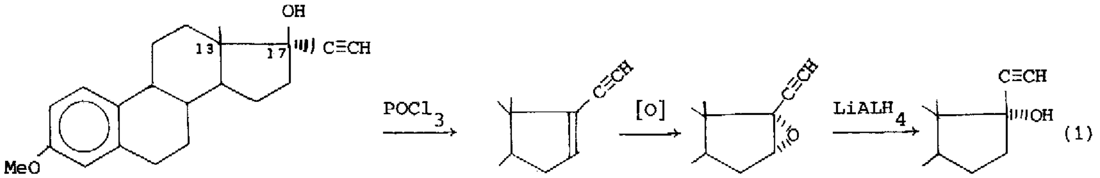
Summary: Epimestranol (**1b**) is obtained in 80% yield from mestranol (**1a**) by converting **1a** into its methanesulfonate **2** and treating **2** with silver(I) nitrate in a mixture of tetrahydrofuran and water.

Although the synthesis of 3-methoxy-17α-ethynyl-17β-hydroxyestra-1,3,5(10)-triene (**1a**, mestranol) by ethynylation of the corresponding 17-ketone is well known,[1] an efficient method for the preparation of its 17-epimer (**1b**, epimestranol) is not available in the literature.

In three papers a low yield synthesis for **1b** has been reported, *viz.* epimerization of mestranol acetate on alumina (yield of **1b**: 5%),[2a,2b] and conversion of **1a** via enyne **3** and epoxide **4** into **1b** (eq. 1; overall yield of **1b**: 6%).[2b,3]



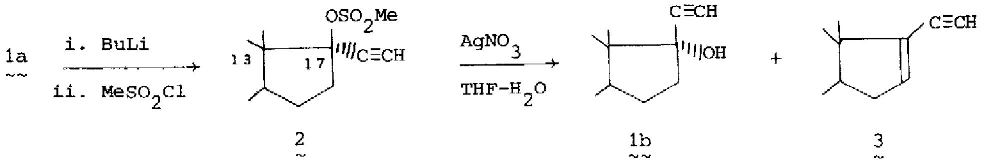
(**1a**) (**3**) (**4**) (**1b**)

In view of our interest in **1b**[4,5] we decided to search for a more attractive route to **1b**. In this paper we wish to present a simple, high yield synthesis of **1b** from readily available **1a**. The strategy we followed to convert **1a** into **1b** is outlined in eq. 2.

As is shown in eq. 2, the method involves the preparation of mestranol methanesulfonate 2. This compound was readily obtained by subsequent treatment of **1a** with n-butyllithium and methanesulfonyl chloride. Although sulfonate esters derived from tertiary alcohols are known generally to be unstable, **2** could be isolated as a crystalline compound [yield: >98%, ^{1}H NMR ($CDCl_3$, δMe_4Si = 0 ppm) data found for **2**: δ0.97(13-Me), 2.70(HC≡), 3.12($MeSO_2O$), 3.78(MeO), and 6.5-7.3(aromatic protons)].

Initial attempts to convert 2 into 1b by H^+-catalysed hydrolysis in, for instance, water containing tetrahydrofuran (THF) were disappointing because of formation of large amounts of enyne 3, a compound which is formed as the main product during the epimerization of mestranol acetate on alumina (*cf.*[2]). In contrast, the Ag^+-catalysed hydrolysis of 1a in $THF-H_2O$ furnished the desired epimer 1b in excellent yield, together with a small amount of enyne 3 (Ratio 1b: 3 ∿ 95:5).

Compound 1b could easily be purified from 3 by treating the crude product with boiling hexane [yield of pure 1b: 80%; $[\alpha]_D^{20}$ (in CH_2Cl_2) + 71.3°; m.p. 139.5-140.0°C (reported[3] 135-136°C); ^1H NMR ($CDCl_3$, δMe_4Si = 0 ppm): δ0.90(13-Me), 2.47(HC≡), 3.78(MeO), 6.5-7.3 (aromatic protons)]



(2)

The experimental procedure is as follows: To a stirred solution of 1a (0.020 mol) and LiBr (0.020 mol) in THF (70 ml) is added at -60°C n-butyllithium (0.020 mol; 1.5 M-solution in n-hexane) followed, after 30 min, by methanesulfonyl chloride (0.020 mol). After stirring for 30 min at -60°C, the reaction mixture is poured into an aqueous NH_4Cl solution (200 ml). Product 2 is isolated by extraction with CH_2Cl_2 (2 x 100 ml), drying of the combined extracts with $MgSO_4$, and, after the addition of pyridine (1 ml), evaporation of the solvent in vacuo at 0°C. The crude crystalline compound is washed with dry diethyl ether (1 x 30 ml). Subsequently, sulfonate 2 is stirred with $AgNO_3$ (0.3 g) in a mixture of THF (30 ml) and distilled H_2O (5 ml) for 2 hrs. at 20°C. The resulting reaction mixture is then poured into an aqueous NH_4Cl solution (200 ml), containing NaCN (2g); crude 1b is isolated as described for 2. The small amount of 3 is removed by treating crude 1b with boiling n-hexane (100 ml), cooling the resulting mixture to 20°C, and filtering off crystalline 1b.

The presented method will probably also be useful for the conversion of other 17α-ethynyl-17β-hydroxysteroids into their interesting 17-epimers.

References

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