Pergamon

Tetrahedron Letters, Vol. 36, No. 8, pp. 1237-1238, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(94)02484-7

A HIGHLY STEREOCONTROLLED APPROACH TO 3-METHOXYESTRA-1,3,5(10),14-TETRAEN-17α-OL, AN IMPORTANT INTERMEDIATE FOR THE SYNTHESIS OF C(14)-SUBSTITUTED STEROID DERIVATIVES.

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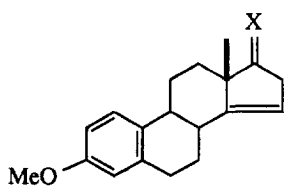
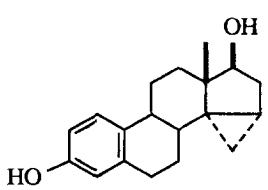
Summary. A four-step reaction sequence including (1) hydroxyl group-assisted epoxidation, (2) Jones oxidation, (3) DIBAH-reduction, and (4) epoxide deoxygenation has been devised in order to effect epimerization of **4** to **1**, the overall yield approaching 65%.

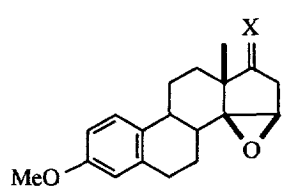
Unique biological properties are occasionally associated with steroid derivatives bearing a substituent other than hydrogen at C(14).[1] Hence, substantial synthetic effort continues to be devoted to C(14)-functionalized target molecules of extraordinarily broad structural diversity.[2] The synthetic potential of the title compound **1**,[3] however, appears to be largely untapped in this context, except for its prominent role in the assemblage of the potent orally active estrogen **2**.[1b] Regrettably, prior art seems to have settled with a notoriously inefficient and laborious route to **1**, a consequence of counterproductive substrate-controlled diastereoface differentiation in the key reductive step, **3**→**1**(10%).[3] Disappointing results for Mitsunobu-type inversion protocols with the readily prepared 17β-hydroxy epimer **4** have similarly conspired against a more widespread use of **1** in steroid synthesis.
The purpose of this communication is to disclose a highly stereocontrolled four-step sequence for the conversion of **4** into **1**, which proceeds in approximately 65% overall yield. This novel approach was based on the reasoning that carbonyl group reduction at C(17) will provide a higher portion of the 17α-hydroxy epimer, if the substrate displays α-concave/β-convex CD-ring topology transiently generated with the aid of a dummy substituent on the steroid β-face at C(14). For obvious reasons of process efficiency, any auxiliary functional group to be attached to C(14) should meet two additional criteria: (1) availability of powerful methodology for its introduction/removal, (2) capability to pre-coordinate and direct certain reducing agents. Since excellent oxirane-assisted carbonyl π-face differentiation has been observed during numerous epoxy ketone reductions utilizing borohydride-based reagents,[4] for example, most requirements stated above appeared to be manageable by a 14β,15β-epoxy group along the **4**→**5**→**6**→**7**→**1** sequence of events.
With this synthetic plan in mind, the starting material **4** was piled up by reduction of either **3**[5] or 17-acetyloxy-3-methoxyestra-1,3,5(10),14,16-pentaene in accord to literature precedent.[3, 6]



1 X= α-OH, β-H
3 X= O
4 X= α-H, β-OH



2



5 X= α-H, β-OH
6 X= O
7 X= α-OH, β-H

Fortunately enough, the modest stereocontrol reported for the epoxidation of **4** with m-chloroperbenzoic acid[7] was overcome by an alternate procedure (toluene, $VO(acac)_2$, TBHP, 22°C, 3.5h; 95%), which operates under strong hydroxyl group participation[4e, 8] to afford the 14β,15β-epoxide **5** exclusively. The next step called for re-adjustment of the ketone oxidation level at C(17), a functional group interconversion most conveniently accomplished under acidic reaction conditions (acetone, Jones reagent, 0°C, 2h; 92%). Some experimentation was necessary to arrive at satisfactory π-facial control in the crucial reductive step, **6**→**7**. Contrary to our expectations, mixtures containing appreciable amounts of the undesired 17β-epimer **5** resulted when the base-sensitive β,γ-epoxy ketone **6** was exposed to various borohydride reagents (MeOH, THF, $NaBH_4$, $CeCl_3 \cdot 7H_2O$, -30°C, 1h; 57%(**7**), 39%(**5**)). The product ratio **7**/**5** was not tremendously responsive to reaction parameters such as concentration, temperature, solvent, or the presence of additives like cerium(III) chloride.[4] Further investigations uncovered the remarkable suitability of diisobutylaluminum hydride (DIBAH) in the current setting, provided that the reaction medium was properly composed. Thus, treatment of a solution of **6** in tetrahydrofuran with DIBAH (toluene, 1.5 molar) at -78°C during 15 minutes delivered **7** in 85% yield and traces of **5** (2%) following chromatographic separation on silica gel (dichloromethane/ethyl acetate, 4:1; gradient elution). The selection of a procedure[9] for epoxide deoxygenation **7**→**1** (THF, WCl_6, n-BuLi, -78→0°C, 1.5h; 92%) was guided by the need for high efficacy paired with superb hydroxyl group compatibility. It is anticipated that the synthetic scheme just outlined will facilitate the stereocontrolled construction of C(14)/C(15)-substituted steroid derivatives, including **2**, via hydroxyl group-directed transformations[4e] in the future.

References and Notes

1. (a) Kirson, I.; Glotter, E. *J. Nat. Prod.* **1981**, *44*, 633. (b) Prousa, R.; Schönecker, B.; Tresselt, D.; Ponsold, K. *J. Prakt. Chem.* **1986**, *328*, 55. (c) Dumbacher, J. P.; Beehler, B. M.; Spande, T. F.; Garraffo, H. M.; Daly, J. W. *Science* **1992**, *258*, 799. (d) Shoji, N.; Umeyama, A.; Motoki, S.; Arihara, S.; Ishida, T.; Nomoto, K.; Kobayashi, J.; Takei, M. *J. Nat. Prod.* **1992**, *55*, 1682. (e) McKee, T. C.; Cardellina, J. H.; Tischler, M.; Snader, K. M.; Boyd, M. R. *Tetrahedron Lett.* **1993**, *34*, 389.
2. (a) Cooper, A. B.; Wright, J. J.; Ganguly, A. K.; Desai, J.; Loebenberg, D.; Parmegiani, R.; Feingold, D. S.; Sud, I. J. *J. Chem. Soc., Chem. Commun.* **1989**, 898. (b) Bull, J. R.; Thomson, R. I. *J. Chem. Soc. Perkin Trans. 1* **1990**, 241. (c) Perez-Medrano, A.; Grieco, P. A. *J. Am. Chem. Soc.* **1991**, *113*, 1057. (d) Gallagher, T. F.; Adams, J. L. *J. Org. Chem.* **1992**, *57*, 3347. (e) Frye, L. L.; Cusack, K. P.; Leonard, D. A. *J. Med. Chem.* **1993**, *36*, 410.
3. Ponsold, K.; Schubert, G.; Wunderwald, M.; Prousa, R. *Pharmazie* **1979**, *34*, 250.
4. (a) Roberts, M. R.; Parsons, W. H.; Schlessinger, R. H. *J. Org. Chem.* **1978**, *43*, 3970. (b) Rücker, G.; Hörster, H.; Gajewski, W. *Synth. Commun.* **1980**, *10*, 623. (c) Oishi, T.; Nakata, T. *Acc. Chem. Res.* **1984**, *17*, 338. (d) Li, K.; Hamann, L. G.; Koreeda, M. *Tetrahedron Lett.* **1992**, *33*, 6569. (e) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.
5. Johnson, W. S.; Johns, W. F. *J. Am. Chem. Soc.* **1957**, *79*, 2005.
6. Rasmusson, G. H.; Arth, G. E. *Steroids* **1973**, *22*, 107.
7. Ponsold, K.; Schubert, G.; Wunderwald, M.; Tresselt, D. *J. Prakt. Chem.* **1981**, *323*, 819.
8. Tanaka, S.; Yamamoto, H.; Nozaki, H.; Sharpless, K. B.; Michaelson, R. C.; Cutting, J. D. *J. Am. Chem. Soc.* **1974**, *96*, 5254.
9. Sharpless, K. B.; Umbreit, M. A.; Nieh, M. T.; Flood, T. C. *J. Am. Chem. Soc.* **1972**, *94*, 6538.

(*Received in Germany* 26 *January* 1994; *accepted* 19 *December* 1994)