Pergamon

Tetrahedron Letters, Vol. 36, No. 25, pp. 4467-4470, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)00754-7

A Total Synthesis of Estradiol and its 6,6-Dimethyl Analogue

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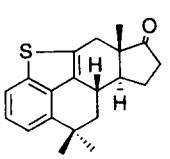
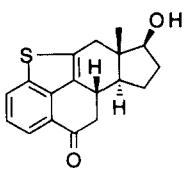
Abstract: A short, stereoselective synthesis of estradiol, and its 6,6-dimethyl analogue, was accomplished from non-steroidal starting materials. A key feature was the use of a benzo[b]thiophene unit to effect (i) the stereoselective formation of the required 8β-H configuration,[2] (ii) the natural steroid configuration at C-9 by desulfurization, and (iii) the regioselective oxygenation at C-3.

We have previously reported the syntheses of 1,11-epithio steroids **1** and **2** as potential agents for the control of estrone dependent breast cancers which featured the diastereoisomerically pure allyl sulfone **3** as a common intermediate.[2] From the outset we recognized that removal of the bridging sulphur atom from these compounds was a potentially simple synthetic route to the estrogens, a class of compounds that continues to attract the attention of synthetic organic chemists because of their important physiological properties, and because the stereochemical problems associated with their structure present stimulating challenges for total synthesis.[3] We now wish to report the successful use of this methodology for the synthesis of ring-A aromatic steroids and 9,11-dehydroestrogens.



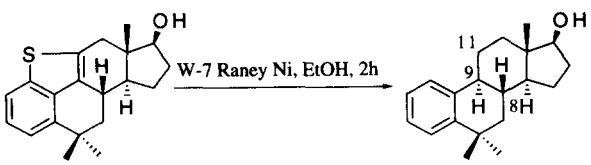
1



2

3 (R=H, Me)

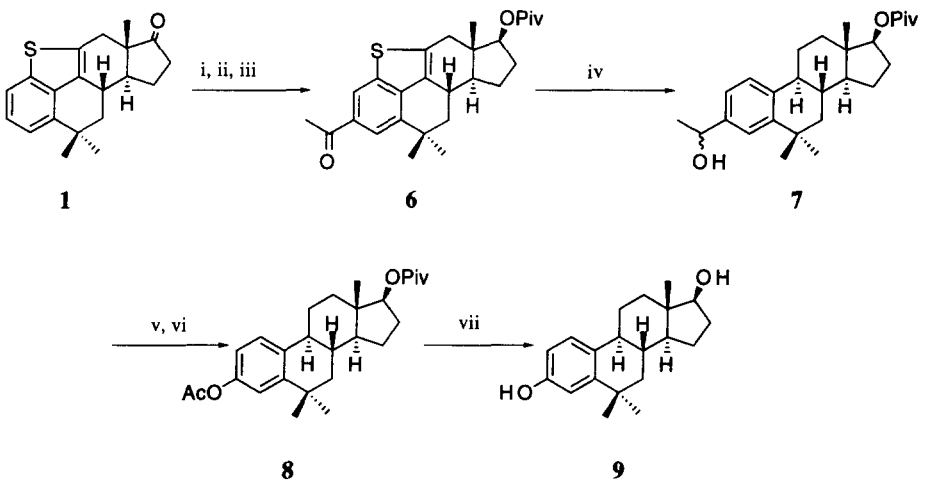
The action of freshly prepared W-7 Raney nickel[4] in boiling ethanol cleanly desulphurized and stereoselectively hydrogenated the alcohol **4** in 70% yield (Scheme 1).[5] NMR analysis unambiguously established that product **5** possessed the natural 9α-H configuration.[6]



4 **5**

Scheme 1

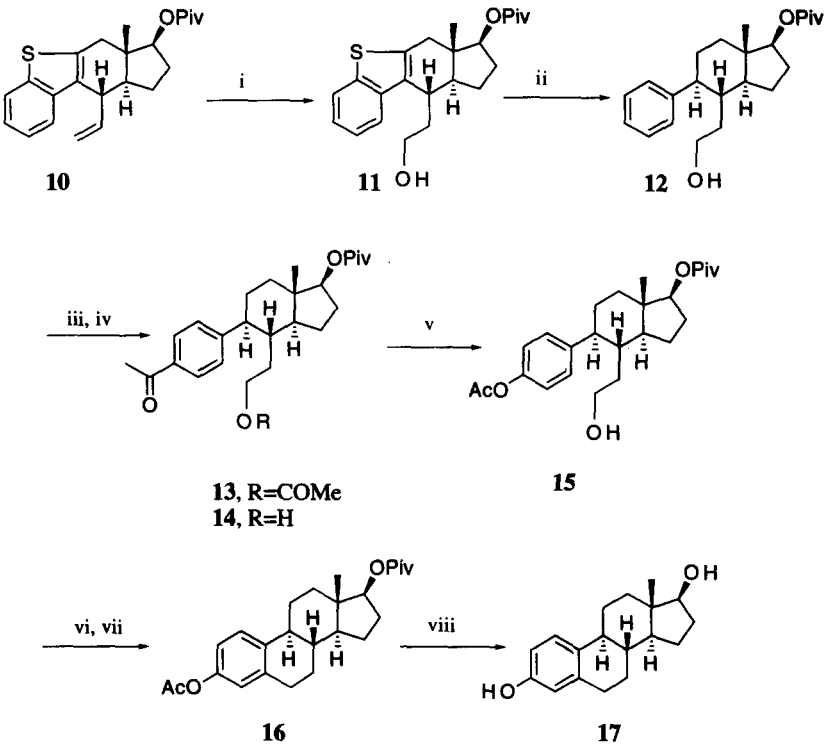
The total synthesis of 6,6-dimethyl estradiol (**9**) is outlined in Scheme 2. Regioselective acylation (97%) of the sulfur bridged steroid **1** was followed by reduction of the 17- ketone (97%) and esterification (96%) to produce the ester **6**. The ester **6** was cleanly desulphurized and hydrogenated to the alcohol **7** upon treatment with W-7 Raney nickel (78%). Barium permanganate oxidation was followed by Baeyer-Villiger oxidation to give the diester **8** (62%, 2 steps) which was reduced with lithium aluminium hydride (89%) to provide the sterol **9** in 19% overall yield (from 2-methylcyclopentenone).[2] The five contiguous stereocentres in the unnatural product **9** were introduced with complete stereoselectivity.



1 **6** **7** **8** **9**

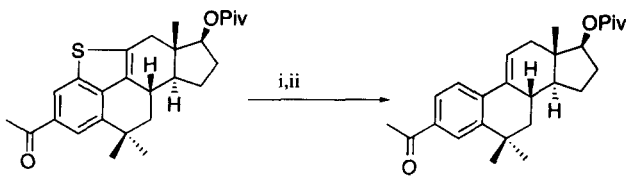
Scheme 2. *Reagents:* i, AcCl (10eq), $SnCl_4$ (4eq), CH_2Cl_2, -78 °C, 30 min; ii, $NaBH_4$ (5eq), methanol, 20 °C, 3 h; iii, $(CH_3)_3COCl$, AgCN, benzene, 78 °C, 2 h; iv, W-7 Raney nickel, ethanol, 78 °C, 1 h; v, $BaMnO_4$ (20 eq), CH_2Cl_2, 20 °C, 8 h; vi, *m*-CPBA (3eq), CH_2Cl_2, 20 °C, 5 d; vii, $LiAlH_4$, ether, 20 °C, 1 h.

(±)-Estradiol (**17**) was prepared in 16% overall yield from 2-methylcyclopentenone as outlined in Scheme 4. Hydroboration of the terminal olefin **10** (97%) gave the primary alcohol **11** which upon treatment with W-7 Raney nickel[5] provided a 14:1 mixture (in 94% yield) of the 9α-H tricyclic compound **12** and its 9β-H isomer. The major isomer **12** was acylated in the *para-* position of the aromatic ring with concomitant acylation of the alcohol function (96%). Saponification of the diester **13** by brief treatment with cold methanolic potassium hydroxide solution afforded the alcohol **14** in 85% yield. Baeyer-Villiger oxidation to the ester **15** was accomplished in 90% yield and the closure of ring-B was effected *via* treatment of the derived mesylate with aluminium chloride in dichloromethane (89%). The diester **16** was reduced with lithium aluminium hydride to give (±)-estradiol (**17**) in 83% yield.[7]



Scheme 3. *Reagents:* i, Monochloroborane.dimethyl sulfide, CH_2Cl_2, 0 °C, 30 min, then H_2O_2, NaOH, THF, bp, 1h; ii, W-7 Raney nickel, ethanol, 78 °C, 3 h; iii, AcCl (10eq), $AlCl_3$ (5eq), CH_2Cl_2, -78 °C to 20 °C, 16 h; iv, KOH, methanol, H_2O, 0 °C, 7 min; v, *m*-CPBA (4eq), CH_2Cl_2, 20 °C, 5 d; vi, Et_3N (1.5eq), MsCl (1.5eq), CH_2Cl_2, 0 °C, 10 min; vii, $AlCl_3$ (7eq), CH_2Cl_2, -78 °C to 20 °C, 3 h; viii, $LiAlH_4$, THF, 20 °C, 1 h.

Treatment of the steroid **6** with aged W-7 Raney nickel,[8] and subsequent barium permanganate oxidation, provided recovered starting material (32%) and the 9,11-unsaturated steroid **18** (45%) (Scheme 4). With regard to this usage, W-7 Raney nickel is reported to act merely as a desulphurizing agent after being boiled with acetone for 2 hours.[9] This is a potentially useful route to the physiologically important 11-substituted cortical steroids.



6 **18**

Scheme 4.*Reagents:* i, W-7 Raney nickel, ethanol, 78 °C, 16 h; ii, $BaMnO_4$ (15 eq), CH_2Cl_2, 20 °C, 3 h.

In conclusion, we have demonstarted the utility of benzo[b]thiophene for the rapid and highly stereoselective synthesis of A-ring aromatic steroids.

Acknowledgements: We thank the SERC for a studentship to M.A.C., and Dr. B.E. Mann for the NMR analysis of the alcohol **5**.

References and Notes

1 Present address: Symphony Pharmaceuticals Inc., 76 Great Valley Parkway, Malvern, PA 19355, USA.

2 Adams, J.P.; Bowler, J.; Collins, M.A.; Jones, D.N.; Swallow, S. *Tetrahedron Lett.* **1990**, *31*, 4355.

3 Blickenstaff, R.; Ghosh, A.; Wolf, G. 'Total Synthesis of Steroids', Academic Press, New York, 1974; Groen, M.B.; Zeelen, F.J.; *Recl. Trav. Chim. Pays-Bas.* **1986**, *105*, 465; Vollhardt, K.P.C.; in 'Strategies and Tactics in Organic Synthesis', Ed. Lindberg, T.; Academic Press, New York, 1984, p 299.

4 Billica, H.R; Adkins, H. *Org. Synth. Coll. Vol.* **III**, 176.

5 Owing to the pyrophoric nature of Raney nickel, care should be taken not to allow the catalyst to become dry when the reaction mixture is filtered.

6 All new compounds gave satisfactory IR, ^1H NMR and MS and/or elemental analysis. Selected NMR data: **5:** ^1H NMR (400 MHz, C_6D_6) δ 2.21 (1H, m, H-9α), 1.61 (1H, ddd, H-8β), 1.51 (1H, dddd, H-11_{ax}). $J^{9,8}$ = 11Hz, $J^{9,11ax}$ = 12Hz, $J^{9,11eq}$ = 4.5Hz, $J^{8,7ax}$ =11Hz, $J^{8,7eq}$ =3Hz; **13:** H-9α (**major isomer**) ^1H NMR (400 MHz, $CDCl_3$) aromatic doublets at δ 7.91 and δ 7.30 (J= 8Hz): **13:** H-9β (**minor isomer**) ^1H NMR (400 MHz, $CDCl_3$) aromatic doublets at δ 7.86 and δ 7.42 (J= 8Hz).

7 (±)-Estradiol (**17**) possessed identical tlc, NMR (400 MHz, acetone-d_6), MS and IR characteristics to those of natural estradiol.

8 The Raney nickel had been prepared 3 months earlier and stored in the refrigerator.

9 Hudlicky, M. 'Reductions in Organic Chemistry', J. Wiley, New York, 1984; Spero, G.; McIntosh, V; Levin, R. *J. Am. Chem. Soc.* **1948**, *70*, 1907.

(*Received in UK* 28 *March* 1995; *revised* 19 *April* 1995; *accepted* 21 *April* 1995)