Pergamon

Tetrahedron Letters, Vol. 35, No. 48, pp. 9025-9026, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01970-3

AN OXY-COPE REARRANGEMENT APPROACH TO C(15) α-ALKYLATED DERIVATIVES OF ESTRADIOL

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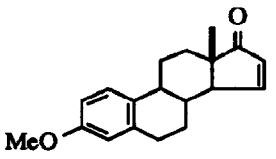
Summary. A stereoselective synthesis of C(15) allyl-substituted estrone derivatives **3** and **4** has been accomplished. Starting with **1** as a common precursor, **3** was made available in two steps by allylmagnesium halide addition to C(17) and subsequent oxy-Cope rearrangement, while the epimer **4** emerged from a Cu(I)-mediated 1,4-addition. The utility of intermediates **3** and **4** is highlighted in the construction of potential estrogen receptor agonists/antagonists **5**, **6**, and **11**.

Structural variations on the steroid backbone involving C(15) have occasionally been drawn upon to arrive at key synthetic intermediates or fascinating drug candidates.[2] Not surprisingly, intriguing members of this group of D-ring modified steroids are also present in nature.[3] A literature survey of synthetic methodology currently available to establish a stereogenic center at C(15) revealed that β-substituted derivatives are, in general, more readily prepared than their α-counterparts.[4] This imbalance primarily originates from a plethora of nucleophiles which enters into kinetically controlled conjugate addition to steroidal enones, like **1**,[5] in a completely β-stereoselective manner. Only in a few instances, the opposite selectivity materialized on a high level, as the corresponding Michael reaction could be run under thermodynamic control.[4d,g] The modest π-face differentiation, however, recently claimed[4h] for certain Cu(I)-promoted 1,4-additions to **1** encourages further work on stereorational approaches to C(15) alkylated steroid derivatives.

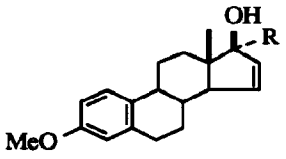
Herein, we complement existing methodology by reporting fully stereocontrolled C(15) α/β-allylations in the estra-1,3,5(10)-triene series and elaborate briefly on a few side-chain transformations to demonstrate the potential of these versatile olefins. Our synthetic scheme exploits a strong bias of C/D ring trans-fused steroidal C(17) ketones to capture organometallic reagents on the α-face anti to the adjacent angular methyl group. Thus, **1** afforded a single tertiary alcohol, **2**, upon treatment with three equivalents of allylmagnesium chloride (THF, 0°C) in 80% yield following chromatography on silica gel (hexane/ethyl acetate, 4:1). With this substrate in hand, the stage was set to relay stereochemistry to C(15) by an anion-accelerated suprafacial [3,3]-sigmatropic shift[6] of the allyl appendage residing at C(17). Gratifyingly, when **2** was exposed to potassium hydride/18-crown-6 in THF at ambient temperature under an inert atmosphere, a smooth oxy-Cope rearrangement ensued to give the unsaturated ketone **3** in 91% yield after chromatographic purification on silica gel (hexane/ethyl acetate, 4:1). The problem of C(15) β-allylation, **1**→**4**, on the other hand, was satisfactorily solved with regard to selectivity and yield utilizing an elegant recent protocol ((a) THF, CuI, LiBr, CH_2CHCH_2MgBr, TMSCl, -78 °C; (b) hydrochloric acid; 73%) due to Lipshutz and co-workers.[7] The assignment of stereochemistry at C(15) in compounds **3** and **4** was confirmed by standard one- and two-dimensional NMR experiments. Readily located in the ^1H NMR spectrum (300 MHz, $CDCl_3$) of **3**, H(14) (δ 1.36 (t, J= 10.8 Hz)) displays a triplet coupling pattern, diagnostic for two vicinal protons (β-H(8), β-H(15)) in a trans-diaxial arrangement. Additional evidence reflecting the close spatial proximity between C(18) methyl group protons and H(15) was provided by NOE spectra of **3**.

At this point, **5**, a first target of biological interest derived from **3**, was obtained by a one-pot procedure including three separate reactions all of which were effected with diisobutylaluminum hydride (toluene, DIBAH, 0-120°C; 84%). A similar operation in the epimeric series delivered the 15β-propyl analogue **6**. Since estrogen receptor

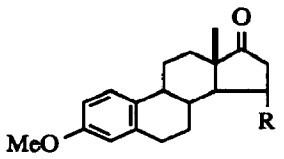
antagonistic properties have been uncovered for certain long-chain bearing analogues of estradiol during the past decade,[8] it was of some interest to probe the behavior of related C(15) substituted derivatives in this context.[4h] The synthesis of a typical example commenced with carbonyl group reduction (MeOH, THF, $NaBH_4$, 0°C; 85%), **3**→**7**, and protection (pyridine, Ac_2O, 22°C; 93%) of the resulting alcohol, **7**→**8**. Subsequent oxidative degradation of the olefinic terminus (Et_2O, THF, H_2O, OsO_4, $NaIO_4$, 22°C; 63%)[9] furnished aldehyde **9**, a useful component for chain extension chemistry based on Wittig reactions. A representative side-chain building block was prepared in three steps by aminolysis of caprolactone (toluene, HN(n-Bu)Me, Me_3Al, 22°C; 46%),[10] bromination (CCl_4, Ph_3P, Br_2, 0°C; 92%), and phosphonium salt formation (Ph_3P, 160°C). Coupling with **9** after ylide generation (DMSO, THF, $Ph_3P^+(CH_2)_5CON(n\text{-}Bu)Me\ Br^-$, t-BuOK, 22°C; 81%) produced a mixture of isomeric olefins, which was subjected to catalytic hydrogenation (EtOAc, Pd/C, H_2, 22°C; 92%) and deprotection (DMF, NaSEt, 120°C; 54%), **10**→**11**.[11]



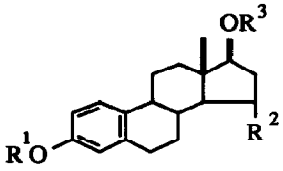
1



2 R= allyl



3 R= α-allyl
4 R= β-allyl



5 R^1= H, R^2= α-propyl, R^3= H
6 R^1= H, R^2= β-propyl, R^3= H
7 R^1= Me, R^2= α-allyl, R^3= H
8 R^1= Me, R^2= α-allyl, R^3= Ac
9 R^1= Me, R^2= α-CH_2CHO, R^3= Ac
10 R^1= Me, R^2= α-$(CH_2)_7CON(n\text{-}Bu)Me$, R^3= Ac
11 R^1= H, R^2= α-$(CH_2)_7CON(n\text{-}Bu)Me$, R^3= H

References and Notes

*Dedicated to Prof. L. A. Paquette on the occasion of his 60th birthday.

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11. Physical data for selected steroids are as follows. **2**: mp 106-108°C (acetone/hexane); $[\alpha]_D$ -76.8° (c 0.52, $CHCl_3$). **3**: mp 79-80°C (acetone/hexane); $[\alpha]_D$ +211.4° (c 0.52, $CHCl_3$). **4**: mp 103-104°C (hexane); $[\alpha]_D$ +80.9° (c 0.52, $CHCl_3$). **8**: mp 108-109°C (acetone/hexane); $[\alpha]_D$ +128.3° (c 0.53, $CHCl_3$). **9**: mp 125-127°C (acetone/hexane); $[\alpha]_D$ +138.2° (c 0.53, $CHCl_3$). **11**: amorphous; $[\alpha]_D$ +116.4° (c 0.51, $CHCl_3$). All $[\alpha]_D$-values were determined at 22°C.

(*Received in Germany* 23 *September* 1994; *accepted* 8 *October* 1994)