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A NEW, STEREOSELECTIVE APPROACH TO C(7)-ALKYLATED ESTRA-1,3,5(10)-TRIENE DERIVATIVES

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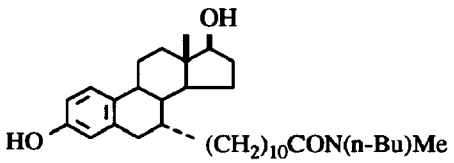
Summary. 17β-Acetyloxy-3-methoxy-6-(phenylsulfonyl)estra-1,3,5(10),6-tetraene (**4**) was prepared as a substrate for conjugate addition of organolithium reagents by a three-step sequence starting from 17β-acetyloxy-3-methoxyestra-1,3,5(10)-trien-6-one (**2**). While methyllithium showed only poor face selectivity, higher alkyllithium species (n-BuLi, t-BuLi) preferred to add to the β-face of **4**. 7α-Substituted derivatives, on the other hand, were generated stereoselectively by utilizing alkynyllithium reagents in the addition step. Removal of the phenylsulfonyl group at C(6) from alkylated products was achieved by conventional reductive desulfonylation methods. A short synthesis of the estrogen receptor antagonist **1** exploiting these observations is presented.

The advent of the first generation of steroidal pure estrogen receptor antagonists which bear a long-chain substituent on the α-face of the estra-1,3,5(10)-triene skeleton at C(7), as exemplified by **1**,[1] has stimulated considerable research activities.[2]



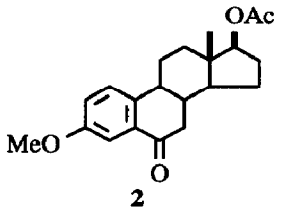
1

From a synthetic point of view, the stereoselective introduction of the substituent at C(7) constitutes the key transformation in the assembly of representatives from this class of steroids. Traditionally, this goal is accomplished by Cu(I)-promoted conjugate addition of properly functionalized organometallic reagents to 17β-hydroxyestra-4,6-dien-3-one or some C(17)-protected derivative thereof.[3] After chromatographic separation from the accompanying unwanted β-epimer, completion of the synthesis requires A-ring aromatization and elaboration of the side-chain terminus.[2a]

In order to improve the accessibility of C(7)-alkylated estra-1,3,5(10)-triene derivatives, we have explored an alternative, reagent-dependent approach which is the subject of this communication.

An efficient conversion of the well-known ketone **2**[4] into vinyl sulfone **4** and the realization of synthetically acceptable levels of stereocontrol in the conjugate addition[5] of organolithium reagents to the electron-deficient double bond in **4** (**4→5a-d**, **4→6a-d**) are the main features of our new procedure.

In an adaptation of a published protocol,[6] **2** was added to a solution of titanium tetrachloride in anhydrous tetrahydrofuran at 0°C, followed by a mixture of thiophenol and triethylamine in the same solvent. Thereafter, stirring was continued at room temperature. Under these reaction conditions, consumption of the starting material had occurred within 30 minutes. Since the desired vinyl sulfide **3** was contaminated with a considerable amount of thioketal (hexane/ethyl acetate, 4:1), elimination of thiophenol was completed by re-submission of the crude product to the action of titanium tetrachloride in tetrahydrofuran at room temperature overnight. Oxidation of the crude vinyl sulfide **3** to the highly crystalline sulfone **4** proceeded uneventfully (AcOH, $NaBO_3 \cdot 4H_2O$, 22°C, 24h).[7] Purification in this sequence of reactions is most conveniently performed at the final stage, where chromatography on silica gel (dichloromethane/ethyl acetate, 9:1) gave **4** in satisfactory 86% overall yield for the three steps.



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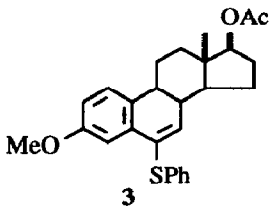

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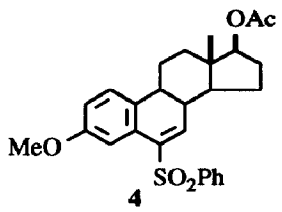

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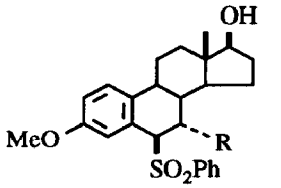
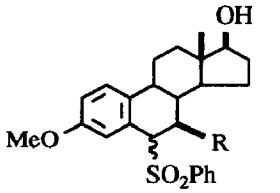
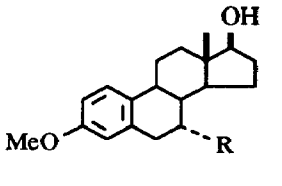


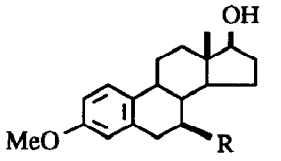
5a-f



6a,b,d: β-SO_2Ph
6c: α-SO_2Ph



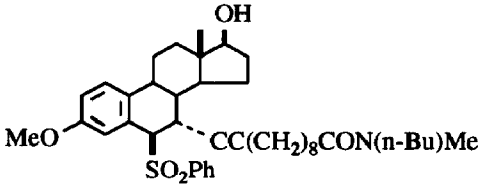
7a-f



8a-c

$HC{\equiv}C(CH_2)_8CON(n\text{-}Bu)Me$

9



10

Table. Product Compositions and Yields for C(7)-Substituted Steroids

	R	5:6	5	6	7	8
a	CH_3	55:45	51%	32%	91%	87%
b	n-C_4H_9	20:80	16%	77%	81%	84%
c	t-C_4H_9	*	*	75%		90%
d	CCTMS	*	90%	*		
e	CCH		90%		90%	
f	C_2H_5		98%		74%	

* only one diastereomer isolated (^1H NMR detection, 300 MHz, $CDCl_3$)

With excess ethereal methyllithium, vinyl sulfone **4** underwent a smooth addition reaction but only partial saponification at C(17) in tetrahydrofuran under an atmosphere of argon at -78°C/-10°C. Consequently, acetate cleavage was completed on the crude product in methanolic potassium hydroxide solution to afford a mixture of isomers **5a** and **6a** (55:45), as judged by ^{1}H NMR spectroscopy (300 MHz, $CDCl_3$).

Upon crystallization of the crude product from toluene, a first crop of homogeneous **5a** (39%) became available. Chromatography of the mother liquor on silica gel eluting with toluene/t-butyl methyl ether (3:2, gradient elution) gave rise to 32% of the 6β,7β-isomer **6a** and an additional amount (12%) of **5a**.

Not unexpectedly, sterically more demanding alkyllithium reagents provide for a better face selectivity in their addition to **4**, albeit in the opposite sense to that of methyllithium. Thus, for the reaction of **4** and n-butyllithium, a product ratio of 1:4 favoring diastereoisomer **6b** was determined by ^{1}H NMR. In a transformation with t-butyllithium, we were even unable to obtain any material **5c** in the 7α-series.

Contrary to these findings, trimethylsilylethynyllithium, prepared either by deprotonation of trimethylsilylacetylene or desilylation of bis(trimethylsilyl)acetylene,[8] displayed a satisfactory preference for attack at the α-face of **4**. Because of its lower reactivity, the alkynyllithium reagent entered into addition to the acceptor double bond at temperatures slightly below 0°C. Saponification of residual acetate and subsequent purification by chromatography on silica gel (toluene/t-butyl methyl ether, 7:3, gradient elution) led to **5d** in 90% yield. No attempts were made to isolate the 6β,7β-diastereoisomer **6d**, which was probably also present as a minor by-product. The saturated ethyl derivative in the 7α-series, **5f**, was prepared by desilylation (CH_3CN, H_2O, CsF, 70°C, 2h; 90%) and catalytic hydrogenation of the triple bond (EtOAc, Pd/C, H_2, 22°C; 98%).

The assignments for newly generated stereogenic centers in addition products **5a-f** and **6a-c** are based on conventional one- and two-dimensional NMR experiments. The structure of isomer **5a**, for instance, is strongly supported by ^{1}H DNOE spectroscopy, which relates the methyl group at C(7) and protons at C(6) and C(9), respectively. Moreover, the coupling pattern of β-H(8) (td, J= 11.0 Hz, J= 3.2 Hz) is also consistent with the presence of a substituent on the α-face at C(7). As expected for isomer **6a**, a nuclear Overhauser enhancement for α-H(9) is absent upon irradiation of the C(7)-methyl protons, but clearly detectable for α-H(6) (d, J= 1.3 Hz). A quartet-like resonance attributed to β-H(8) reflects a trans-diaxial-type arrangement of this atom and three vicinal coupling partners α-H(9), α-H(14), and α-H(7). Close similarities in the NMR spectral parameters of compounds **5b-f/6b-c** to either those of **5a** or **6a** render structure determinations in these two classes of homologous steroids a straightforward task.

The next step in our synthetic scheme called for reductive desulfonylation at C(6) (**5a-f→7a-f**, **6a-c→8a-c**). Except for the ethynyl derivative **5e** (MeOH, 3%Na(Hg), Na_2HPO_4, 0°C, 2h; 90%),[9] this transformation was routinely effected by metal-ammonia reduction (NH_3, Li, -50°C; NH_4Cl) in yields ranging from 74-91%.

Capitalizing on the knowledge gained from the study delineated above, a short synthesis of **1** and other analogues of interest could now be reduced to practice. Toward this end, amide **9** which resulted from condensation of undec-10-ynoic acid and n-butylmethylamine was deprotonated by treatment with methyllithium in tetrahydrofuran during a total of 30 minutes, first at -78°C, then at -20°C. The addition reaction between the resulting acetylide species and vinyl sulfone **4** was subsequently conducted at -10/0°C for 1h to furnish **10** in 57% yield after quenching with aqueous ammonium chloride, saponification of the crude reaction mixture in methanolic potassium hydroxide solution, and chromatography on silica gel (toluene/ethyl acetate, gradient elution). Catalytic reduction of the triple bond (EtOAc, Pd/C, H_2, 22°C; 80%), reductive desulfonylation (MeOH, 3%Na(Hg), Na_2HPO_4, 0°C, 2h; 93%), and cleavage of the methyl ether (DMF, $NaSCH_3$, 130°C, 15h; 65%) was all that remained to finish the synthesis of **1**.[10]

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10. Physical data for selected steroids are as follows. **4**: mp 148-150°C (acetone/hexane); $[\alpha]_D^{22}$ -59.6° (c 0.51, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.92-7.90 (m, 2H), 7.57-7.44 (m, 4H), 7.40 (s, 1H), 7.13 (d, J= 8.5 Hz, 1H), 6.77 (dd, J= 8.5 Hz, J= 2.7 Hz, 1H), 4.75 (dd, J= 9.0 Hz, J= 7.8 Hz, 1H), 3.73 (s, 3H), 2.08 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 158.0, 143.7, 140.5, 138.9, 133.2, 131.9, 129.1, 128.3, 127.5, 125.0, 114.2, 110.9, 82.0, 55.3, 47.3, 43.5, 40.5, 39.1, 36.0, 27.3, 24.2, 23.1, 21.2, 11.7. **5a**: mp 209-211°C (toluene); $[\alpha]_D^{22}$ -38.5° (c 0.52, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.61-7.41 (ser m, 5H), 7.21 (d, J= 8.7 Hz, 1H), 6.96 (d, J= 2.8 Hz, 1H), 6.88 (dd, J= 8.7 Hz, J= 2.8 Hz, 1H), 4.10 (s, 1H), 3.75 (s, 3H), 3.70-3.63 (m, 1H), 1.38 (d, J= 6.2 Hz, 1H), 0.86 (d, J= 7.2 Hz, 3H), 0.56 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.2, 138.9, 133.5, 133.2, 129.2, 128.9, 127.2, 126.4, 116.8, 115.9, 81.6, 73.1, 55.3, 46.5, 43.5, 37.4, 36.6, 35.5, 30.5, 28.9, 26.3, 22.2, 13.0, 11.3. **6a**: mp 175-176°C (acetone/hexane); $[\alpha]_D^{22}$ -87.7° (c 0.52, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.62-7.41 (ser m, 5H), 7.17 (d, J= 8.5 Hz, 1H), 6.81 (dd, J= 8.5 Hz, J= 2.7 Hz, 1H), 5.97 (d, J= 2.7 Hz, 1H), 3.85 (d, J= 1.3 Hz, 1H), 3.78-3.71 (m, 1H), 3.50 (s, 3H), 1.45 (d, J= 5.9 Hz, 1H), 1.15 (d, J= 6.9 Hz, 3H), 0.73 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.1, 137.2, 136.7, 133.5, 129.3, 128.7, 128.3, 125.1, 116.5, 114.9, 81.4, 75.7, 55.1, 51.3, 45.6, 43.8, 39.4, 36.1, 32.2, 30.5, 25.2, 25.2, 11.2. **8c**: mp 149-150°C (acetone/hexane); $[\alpha]_D^{22}$ -76.2° (c 0.53, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.04 (d, J= 7.8 Hz, 1H), 6.73-6.70 (m, 2H), 3.79 (s, 3H), 2.85 (dd, J= 14.7 Hz, J= 1.1 Hz, 1H), 2.55 (dd, J= 14.7 Hz, J= 6.7 Hz, 1H), 1.43 (d, J= 6.1 Hz, 1H), 0.90 (s, 3H), 0.57 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.7, 141.8, 134.3, 123.0, 113.4, 110.2, 82.2, 55.3, 51.6, 45.0, 44.8, 44.7, 39.1, 37.4, 34.4, 30.5, 30.4, 29.1, 24.9, 24.7, 11.7.

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