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Bridged androstenediol analogs as ER-β selective SERMs

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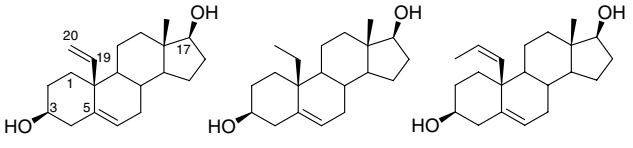
Abstract—A series of bridged androstenediol derivatives was prepared. The bridged compounds exhibited reduced ER-β selectivity relative to uncyclized analogs.

The clinical significance[1a] of selective estrogen receptor modulators (SERMs) and the search for novel SERMs[1,2] are well documented. Reports of a second ER receptor subtype[3] prompted interest in both ER-α[4] and ER-β[5] subtype-selective SERMs. Non-steroids predominate but several steroidal SERMs have also been reported.[6] We have described non-selective spiroindenes,[2a] ER-α-selective dihydro-benzoxathiins,[4a,b,c] and ER-β-selective androstenediols[5a] as SERMs.



1 **2** **3**

Molecular modeling of the substituted androstenediol **1** bound in ER-β indicated that it adopts a conformation in which the C-19 substituent is located above the steroid A–B ring junction (the proposed binding conformation of **1** was confirmed by X-ray analysis).[5a] We speculated that locking the molecule in this conformation by bridging the C-19 substituent to C-4, as in analog **8**, for example, might result in compounds with improved ER-β binding affinity and selectivity.

The 20-*cis*-methyl analog **3** retains binding affinity and selectivity comparable to that of **1** and **2**, and is superior to the corresponding propyl analog,[5a] suggesting that the additional carbon atom present in **8** and **9** would be tolerated. We anticipated that **8** and **9** would be accessible by applying olefin metathesis technology to a C-4 allylated precursor such as **6**.

Silylation of **1** followed by selective deprotection and oxidation of the C-3 hydroxyl group afforded enone **5**,[7] which could be deprotected to afford the testosterone analog **4** (Scheme 1).[5a] Alkylation of enone **5** followed by reduction of the enone to the Δ-5 alcohol[8] afforded the key intermediate **6**. Because the use of the patented Grubbs ruthenium-based olefin metathesis catalysts[9] required a license for use in drug discovery, we turned our attention to an alternative molybdenum-based catalyst reported earlier by Schrock and co-workers.[10a] Although the air sensitivity and lower functional group tolerance of the Schrock catalyst render it inferior to the newer Grubbs catalyst for some applications, the Schrock catalyst proved to be adequate for our purpose. Protection of the 3-OH of **6** as the TBDMS ether, followed by olefin metathesis using the Schrock catalyst,[10b] and deprotection with HF/pyridine afforded the desired cyclic analog **8** in reasonable overall yield. The structure of **8** was confirmed by NMR analysis. HMBC was especially useful in confirming the carbon skeleton of **8** and the other bridged analogs described herein. Key HMBC correlations observed for **8** were H-3 → C-21, H-20 → C-10 and C-4, H-21 → C-4 and C-3, and

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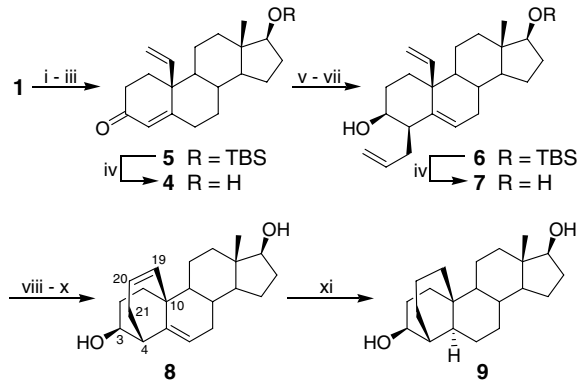
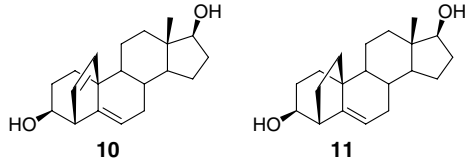
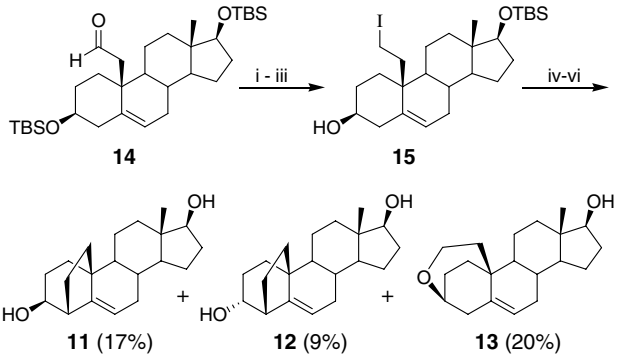


Scheme 1. Reagents and condition: (i) TBDMS–Cl, imidazole, DMF, 77%; (ii) *n*-Bu4NF, THF, 69%; (iii) $Al(O^iPr)_3$, *N*-Me-piperidin-4-one, toluene, 75%; (iv) HF, pyridine; (v) KO–^{t}Bu, *t*-BuOH, allyl bromide, reflux, 53%; (vi) Ac2O, NaI, TMS–Cl, 53%; (vii) $NaBH_4$, EtOH, 74%; (viii) TBDMS–Cl, imidazole, DMF, 93%; (ix) Schrock catalyst,[10] benzene, 90%; (x) HF, pyridine, 89%; (xi) H_2, Pd/C, EtOAc, 53%.

H-4 → C-10 and C-21. In addition, COSY and NOE correlations were observed for H-4 → H-21. We had hoped that we could selectively hydrogenate the disubstituted C-19,20 olefin in the presence of the trisubstituted C-5,6 olefin to prepare the direct cyclic analog of **2** (with the C-5,6 olefin intact). Unfortunately, hydrogenation of **8** afforded only the fully saturated analog **9**.

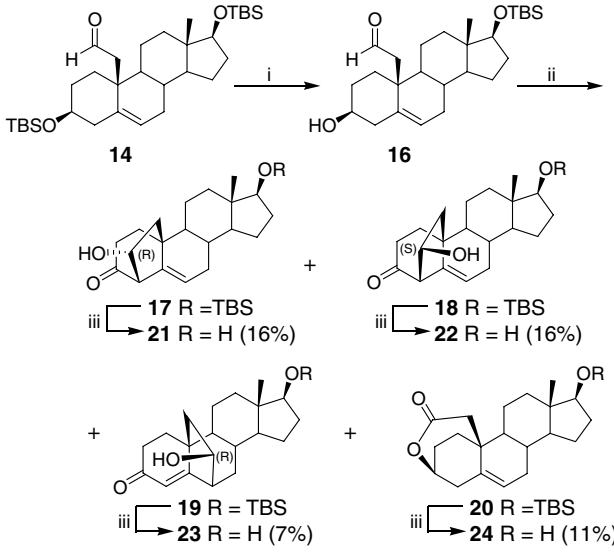


In addition to the three-carbon bridged analogs **8** and **9**, we also targeted the two-carbon bridged compounds **10** and **11**, in which the C-20 carbon is directly linked to C-4. The C-19,20 saturated analog **11** proved to be the more synthetically accessible of the two and was readily prepared from the bis-protected aldehyde **14**[5a] (Scheme 2). Reduction of the aldehyde followed by iodination and deprotection afforded intermediate iodide **15** in 47% overall yield. Oppenauer oxidation of **15** resulted in oxidation to the 3-ketone which cyclized in situ to afford the bridged ketone. Subsequent reduction with $NaBH_4$ afforded a mixture of bridged alcohols **11** and **12**. Cyclic ether **13**, formed as a by-product during the Oppenauer oxidation, was also isolated. The structures of **11**–**13** were confirmed by NMR analysis. The carbon skeletons of **11** and **12** were established by observation of an H-3 → C-4 → C-20 → C-19 correlation in an HMQC-TOCSY experiment. Stereochemistry at C-3 was established by coupling constants and by observation of an NOE from H-3 → H-20 in **12**. Key HMBC correlations observed for **13** were H-3 → C-20 and H-20 → C-3.

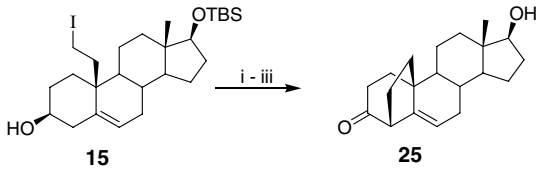


Scheme 2. Reagents: (i) $NaBH_4$, EtOH, 97%; (ii) I_2, PPh_3, imidazole, toluene, 90%; (iii) Bu_4NF, THF, 60% (+13% diol); (iv) $Al(O^iPr)_3$, *N*-Me-piperidin-4-one, toluene; (v) pyr·HF, THF; (vi) $NaBH_4$, MeOH.

Aldehyde **14** was also an intermediate in our attempt to synthesize the unsaturated 2-carbon bridged analog **10**. Selective desilylation of the 3-hydroxyl afforded **16** (Scheme 3). Oxidation to the 3-ketone proceeded with concomitant cyclization to afford three aldol products **17**–**19**. Interestingly, cyclization occurred at both C-4 and C-6, in contrast to the iodide cyclization (Scheme 2) which resulted in cyclization at C-3 only, possibly due to the irreversible nature of the iodide cyclization. Lactone **20**, formed by oxidation of the cyclic hemiacetal, was also isolated. Unfortunately, all attempts to dehydrate **17**–**19** failed and we were unable to obtain **10**. Deprotection of **17**–**20** afforded the corresponding alcohols **21**–**24** for testing.



Scheme 3. Reagents: (i) *n*-Bu_4NF, THF, 69%; (ii) Dess–Martin periodinane, CH_2Cl_2; (iii) HF, pyridine.



Scheme 4. Reagents: (i) Dess–Martin periodinane, solvent, 66%; (ii) Rieke Mg, THF, 60 °C, 77%; (iii) *n*-Bu4NF, THF, 75%.

Compound **25**, the C-20 deoxygenated analog of **21** and **22**, was prepared from iodide **15** (Scheme 4). Oxidation of **15** followed by treatment of the resulting ketone with Rieke magnesium[11] afforded a bridged analog with a 2-carbon bridge to C-4 (instead of the anticipated Grignard formation followed by addition to the C-3 ketone) which was deprotected to afford **25**.

The novel steroids were evaluated in an estrogen receptor–ligand binding assay (Table 1).[12] Although all of the new compounds are weaker ER ligands than **1**–**3**, the active bridged analogs are all ER-β selective albeit less so than **1**–**3**. The most interesting bridged analogs are **8**, with a 3-carbon unsaturated bridge, and **11**, with a 2-carbon saturated bridge. The ER-α binding affinity of **8** is unchanged relative to **1** but ER-β binding affinity is reduced by an order of magnitude relative to the open-chain compound **1**. Similarly, compared to the *cis*-methyl analog **3**, the bridged analog **8** has about the same affinity for ER-α but much reduced affinity for ER-β results in a large reduction in selectivity. Hydrogenation of the olefins present in **8** to afford the fully saturated analog **9** results in another 2-fold reduction in binding affinity for both receptors, resulting in a weaker ligand with unchanged selectivity. By contrast, the saturated 2-carbon analog **11** exhibits substantially increased ER-α binding affinity relative to the open-chain analog **2** which combines with a smaller reduction in ER-β affinity to give a much reduced ER-β selectivity (146X observed with **2** to only 6X for **11**). As expected, the 3-epimer **12** is a weaker ligand than **11** for both receptors. Interestingly, the hydroxylated bridged analogs **21**–**23** were completely inactive in the binding assay. Of course, these compounds also lack the important C-3 hydroxyl group which probably accounts for most of the reduction in binding affinity. However, the corresponding de-oxy analog **25** retained significant ER-β activity, suggesting that at least some of the reduction in binding is due to the C-20 hydroxyl.

New compounds were also evaluated in a cell-based transactivation assay to measure estrogen agonism in HEK293 cells.[13] Once again, **8** and **11** were the most noteworthy analogs. Interestingly, **8** is slightly more ER-β selective in the transactivation assay than in the ligand binding assay, while **11** is less selective in the transactivation assay than in the binding assay although the changes are relatively small. Once again, analogs **21**–**23** were devoid of activity.

The bridged analogs were further evaluated for binding to the androgen receptor (AR).[14] Compared to the lead compound **1**, which was a 33 nM ligand for AR, the novel bridged analogs were generally weaker ligands for AR. Interestingly, the bridged analog **11** had the best AR/ER-β ratio since its ER-β affinity decreased to a much lesser extent than its AR affinity. Surprisingly, the allylated analog **7** actually exhibited an increase in

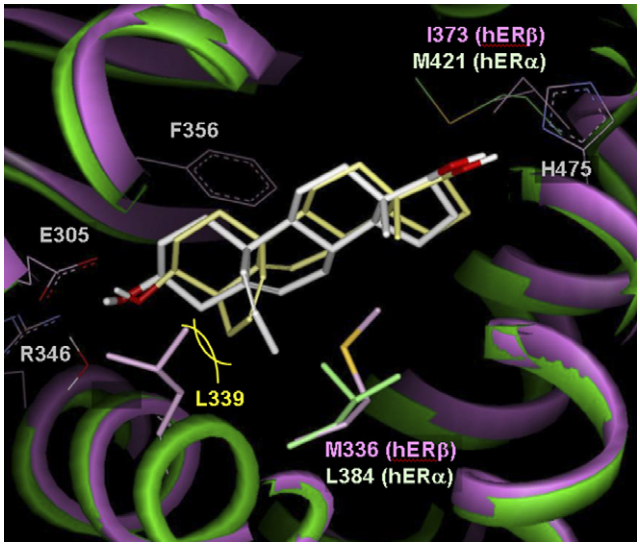


Figure 1. Superposition of 3-carbon unsaturated bridged analog **8** (yellow) and 19-*cis* methyl compound **3** (white) analogs in the context of hER-α (green) and hER-β (purple) complexed with compound **1**. Residue numbering is that of hER-β. The yellow arcs represent the steric clash with Leu339.

Table 1. Biodata

Compound	ER binding (IC_{50}, nM)[12]			ER transactivation (EC_{50}, nM)[13]			AR (IC_{50}, nM)[14]	
	hER-α	hER-β	α/β	α	β	α/β	AR	AR/ER-β
1	2240	11	204	980	4	245	33	3
2	2330	16	146	—	—	—	88	5.5
3	1956	16	126	344	21	16	718	45
4	>10,000	782	>12	>1000	379	>2.6	7.9	0.01
7	>10,000	3020	>3	>1000	>1000	1	15	0.005
8	2240	157	14	4893	132	37	85	0.5
9	4990	322	15	1300	219	6	68	0.2
11	317	50	6	44	28	2	1375	28
12	8135	854	10	435	198	2	1120	1.3
13	>10,000	>10,000	1	>1000	440	>2	710	<1
21	>10,000	>10,000	1	>1000	>1000	1	>1000	1
22	>10,000	>10,000	1	>1000	>1000	1	>1000	1
23	>10,000	>10,000	1	>1000	>1000	1	>1000	1
24	>10000	>10,000	1	>1000	>1000	1	>1000	1
25	>10,000	1460	>7	407	86	5	—	—
Estradiol	1.4	1.2	1.2	0.75	2.1	2.8	19.1	16
Testosterone	>10,000	>10,000	1	—	—	—	2.7	<0.0002

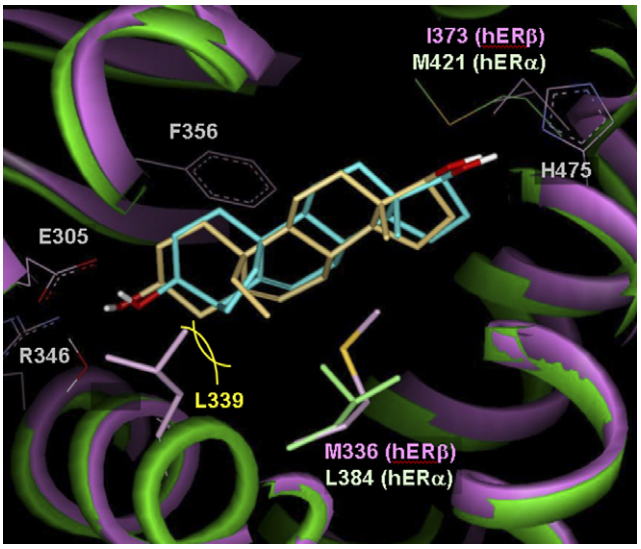


Figure 2. Superposition of 2-carbon saturated bridge compound **11** (cyan) and 10-ethyl compound **2** (orange) analogs in the context of hER-α (green) and hER-β (purple) complexed with compound **1**. Residue numbering is that of hER-β. The yellow arcs represent the steric clash with Leu339.

AR binding affinity which, coupled with a substantial decrease in ER-β affinity, makes **7** a very AR-selective compound, comparable to the testosterone analog **4**.

Molecular modeling of compounds **8** and **11** provides a rationale for their reduced ER-β selectivity relative to the open-chain analogs **3** and **2** (Figs. 1 and 2).[15] The bridging atoms of compounds **8** (Fig. 1) and **11** (Fig. 2) have a negative steric interaction with the side chain of Leu339 that pushes the molecules lower in the binding pocket, and reduces their ER-β binding affinity relative to their non-bridged analogs **3** and **2**.

Due to its increased steric bulk the three-carbon bridge of **8** has a more unfavorable interaction with Leu339 than the two-carbon bridge of **11**, resulting in a slightly larger decrease in ER-β affinity for **8**. At the same time, tying the C-10 substituent of **11** back with the bridge results in a diminished interaction with the side chain of Leu384 of ER-α, which results in a smaller decrease in ER-α affinity for **11** versus **2**. Since the high ER-β selectivity of **2** is largely due to the negative steric interaction of the 10-ethyl group with this ER-α side chain,[16] the bridged analog **11** has substantially reduced selectivity for ER-β.

In conclusion, the bridged androstenediol analogs described herein are generally weaker ligands than the open-chain analogs and are less selective for ER-β as well. Additional studies on the SAR of steroidal SERMs will be reported in future communications from this laboratory.

Acknowledgments

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15. (a) Models were built using the crystallographic coordinates of compound **1** as cocrystallized with hER-β (Fitzgerald et al., manuscript in preparation). Energy minimization for all of the models within context of the hER-β receptor (**1** cocrystallized) was accomplished by rigidly fixing all residues except for side chains which fell within 5 of the modeled ligand which were allowed to minimize in conjunction with the ligand. All minimizations were conducted using the MMFFs forcefield[15b] with a distance-dependent dielectric model of 2*r*; (b) Halgren, T. A. *J. Comput. Chem.* **1999**, *20*, 730.
16. The terminal carbon of the ethyl group for ER-β-selective compound **2** is 2.4 away from C-5 of Leu384 in ER-α, which is about 1.0 closer than the distance to the S of Met336 in ER-β. This negative steric interaction with Leu384 in hER-α results in decreased affinity for ER-α with a corresponding increase in ER-β selectivity. The bridging atoms for compound **11** are further away from Leu384 (3.7) and are expected to have less of a negative interaction.