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2-Phenylspiroindenes: A Novel Class of Selective Estrogen Receptor Modulators (SERMs)

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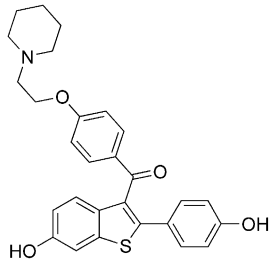
Abstract—A series of 2-phenylspiroindenes was prepared. The most active analogue (**2**) was found to be comparable in potency to raloxifene (**1**) as an estrogen receptor ligand.

Hormone replacement therapy (HRT) is widely used to treat a variety of conditions, such as hot flashes and osteoporosis, resulting from estrogen deficiency in postmenopausal women.[1] Although HRT is very effective, it is also associated with some serious side-effects, including blood clots and increased risk of cancer. The selective estrogen receptor modulators (SERMs) have generated considerable interest due to their potential ability to provide the benefits of estrogen without the associated liabilities.[2] The utility of SERMs is exemplified by the use of Tamoxifen[3] for the prevention and treatment of breast cancer and raloxifene (**1**)[4] for the treatment and prevention of osteoporosis.[4d,e] Several additional SERMs, such as lasofoxifene,[5] fulvestrant,[6] EM-652,[7] ERA-923,[8] and TSE-424[8] are in late stages of clinical trials for a variety of indications. Although the current SERMs have clear advantages over conventional HRT, they retain some of the disadvantages as well. Clearly, an 'ideal SERM' has not yet emerged.

We became interested in SERMs several years ago and chose to focus initially on raloxifene isosteres. It was known from X-ray crystal studies that the active conformation of raloxifene (**1**) was one in which the phenylketone at C-3 of the benzothiophene was orthogonal to the benzothiophene ring rather than coplanar.[4c,f] It has been hypothesized that locking the aromatic rings in this relative configuration by fusing the pendant phenyl ring and the carbonyl linker might result in an especially active compound.[4b] We speculated that this might also be accomplished by constructing a spiroindene system such as **2**. Molecular modelling studies showed that **2** would overlap nicely with the active conformation of raloxifene. We chose the simplified analogue **3** as our initial synthetic target.



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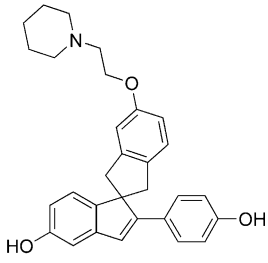

2

The synthesis of **3** was accomplished using the synthetic route outlined in Scheme 1.[9] Alkylation of commercially available anisindione **4** with methyl α-bromophenylacetate **5** under basic conditions afforded the desired alkylation product **6** in excellent yield (90% yield of recrystallized product on 1.26 g scale). Hydrogenation of **6** not only reduced the ketones but also resulted in hydrolysis of the methyl ester to the desired carboxylic acid **7** (due to lactonization of the intermediate benzylic hydroxyl to form a lactone followed by hydrogenolysis of the resulting benzylic ester) in very good yield (74% yield of crystalline product on 1.70 g scale). Conversion of acid **7** to the acid chloride by reaction with PCl_5 followed by $AlCl_3$ catalyzed Friedel–Crafts cyclization afforded the desired ketone **8** in low and variable yield

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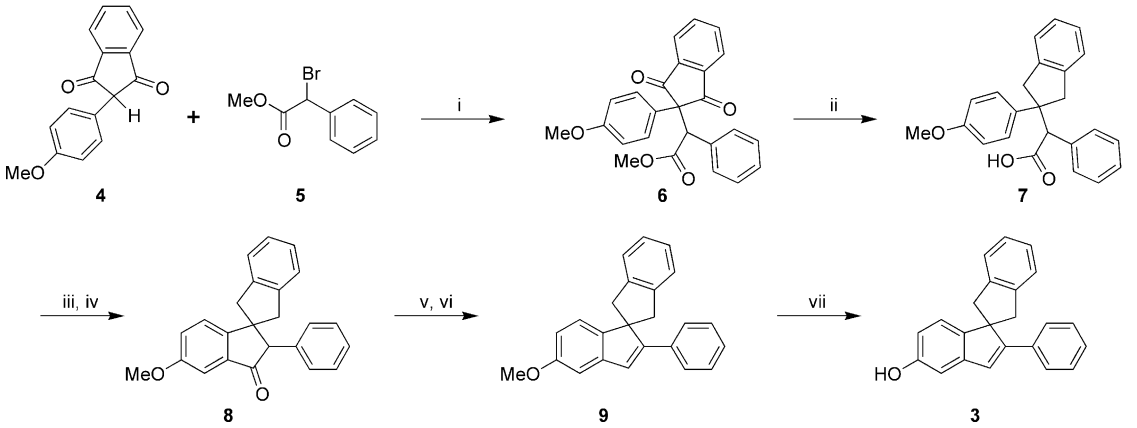


Scheme 1. Reagents and conditions: (i) K_2CO_3, DMF, 50 °C, 15 m, 90%; (ii) H_2, $Pd(OH)_2/C$, EtOAc, EtOH, AcOH, 68 h, 74%; (iii) PCl_5, CH_2Cl_2, 0 °C, 1 h; (iv) $AlCl_3$, CH_2Cl_2, 0 °C, 45 m, 25% from **7**; (v) $NaBH_4$, MeOH, THF, 14 h; (vi) TsOH, benzene, reflux, 2 h, 12–24% from **8**; (vii) BBr_3, CH_2Cl_2, 2 h, 40%.

(**8** appears to be unstable to chromatography, perhaps due to residual HCl generated in the cyclization). Reduction of the ketone with $NaBH_4$ followed by acid-catalyzed dehydration yielded olefin **9**. Finally, removal of the methyl ether protecting group with BBr_3 afforded the desired spirocycle **3**. Despite the fact that **3** is a relatively simple analogue of raloxifene, lacking both the second phenolic hydroxyl group and the basic side chain, it had very good activity in an ER binding assay (Table 1). We were therefore encouraged to continue in this area.

We next turned our attention to the more complex analogues **10** and **11**, which each have an additional phenolic hydroxyl group. Compounds **10** and **11** were prepared by the routes outlined in Schemes 2 and 3, respectively. Reaction of **4** with **12** (prepared in essentially quantitative yield by NBS bromination of commercial methyl 4-methoxyphenylacetate)[10] afforded the desired alkylation product **13** in quantitative yield. Hydrogenation of **13** not only reduced the ketones but also resulted in hydrolysis of the methyl ester to the desired carboxylic acid **14** in modest yield. The yield was a bit lower than usual in this case due to incomplete reduction (some monoketone was isolated as a by-product). Conversion of acid **14** to the acid chloride by reaction with PCl_5 followed by $AlCl_3$ catalyzed Friedel–Crafts cyclization afforded the desired cyclic ketone **15** which was immediately reduced with $NaBH_4$ followed by acid-catalyzed dehydration to afford the penultimate intermediate **16** in 13% overall (for the four steps from **14**) yield. Removal of the methyl ether protecting groups with BBr_3 afforded the desired spiroindene **10** in 54% yield.

Similarly, reaction of **4** with **17** (prepared in essentially quantitative yield by NBS bromination of commercial methyl 3-methoxyphenylacetate)[10] afforded the desired alkylation product **18** in excellent yield. Hydrogenation of **18** afforded the desired carboxylic acid **19** in 72% recrystallized yield. Conversion of acid **19** to the acid chloride by reaction with PCl_5 followed by $AlCl_3$ catalyzed Friedel–Crafts cyclization afforded the desired cyclic ketone **20** which was immediately reduced with $NaBH_4$ followed by acid-catalyzed dehydration to afford the penultimate intermediate **21** in 6% overall (from **19**) yield. Removal of the methyl ether protecting groups with BBr_3 afforded spiroindene **11** in 80% yield.

We were very pleased to find that **10** was significantly more active than **3** in the ER binding assay (Table 1). Interestingly, though, the meta substituted analogue **11** was slightly less active than **3** despite the presence of the additional hydroxyl group.

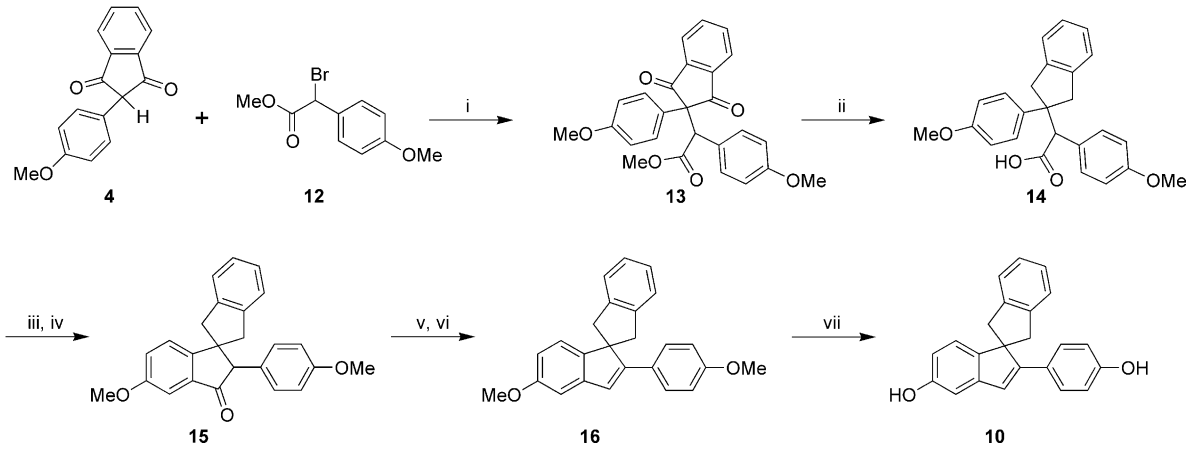
The availability of ketone **15**, an intermediate in the synthesis of **10**, allowed us to explore the effect of alkyl substitution at C-3 of the spiroindene. Reaction of **15** with methylmagnesium chloride followed by dehydration with *p*-toluenesulfonic acid afforded the 3-methyl-spiroindene **22** in low yield. Deprotection of **22** then provided the desired 3-methylspiroindene diol **23**. Introduction of the methyl group at C-3 resulted in a slight decrease in ER binding affinity (Scheme 4).

The low overall yield of the synthetic routes outlined in Schemes 1–3 prompted us to examine an alternative route. It has been reported that indene can be di-alkylated with a dibromide under basic conditions to afford spiroindenes.[11] We hypothesized that this route could be applied to 2-phenylindenes to afford compounds like **2**. Indeed, reaction of 2-phenylindene **24** with α,α′-

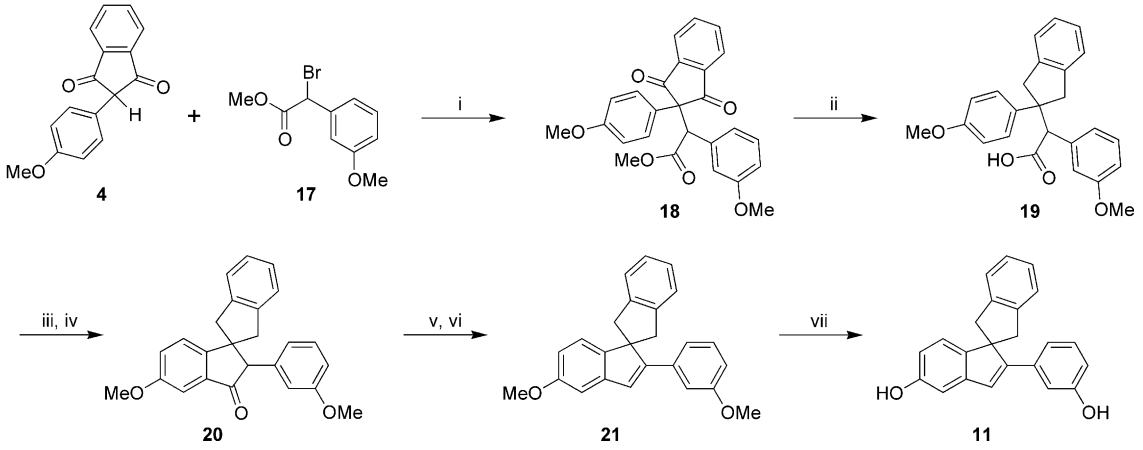
Table 1. Estrogen receptor binding affinities (IC_{50})

Compd	Binding affinity IC_{50} (nM)[a]			
	Human ERα	Human ERβ	Rat ERα	Rat ERβ
1	1.8	12	0.7	3.4
2	1.0	1.9	1.7	2.7
3	24	21	ND	ND
10	4.3	2.1	ND	1.1
11	28	23	34	29
23	19	5.9	2.2	1.2
26	>10,000	>10,000	>10,000	>10,000
28	58	429	114	1070
34	31	12	16	15

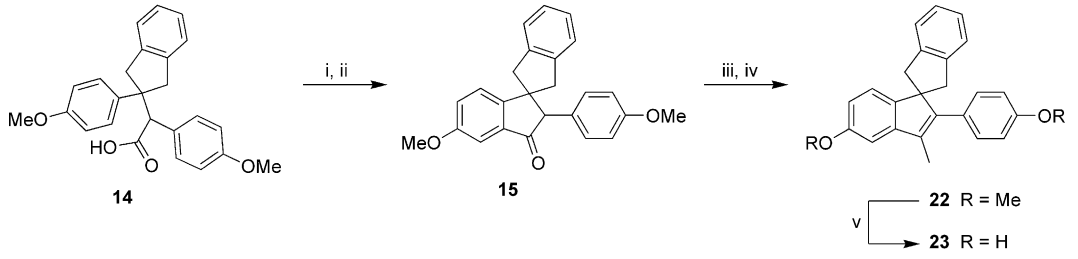
[a]The IC_{50} values were generated in an estrogen receptor ligand binding assay. This scintillation proximity assay was conducted in NEN Basic Flashplates using tritiated estradiol and full length recombinant human ER-alpha and ER-beta proteins.



Scheme 2. Reagents and conditions: (i) K_2CO_3, DMF, 50 °C, 15 m, 100%; (ii) H_2, $Pd(OH)_2/C$, EtOAc, EtOH, AcOH, 23 h, 44%; (iii) PCl_5, CH_2Cl_2, 0 °C, 1 h; (iv) $AlCl_3$, CH_2Cl_2, −20 °C, 1 h then 0 °C, 75 m; (v) $NaBH_4$, MeOH, THF, 2.5 h; (vi) TsOH, benzene, reflux, 2 h, 13% from **14**; (vii) BBr_3, CH_2Cl_2, 2 h, 54%.



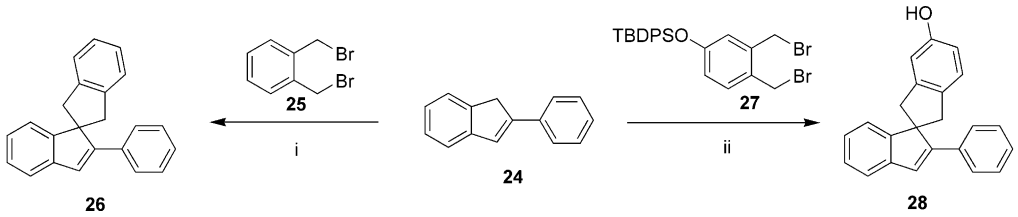
Scheme 3. Reagents and conditions: (i) K_2CO_3, DMF, 50 °C, 20 m, 88%; (ii) H_2, $Pd(OH)_2/C$, EtOAc, EtOH, AcOH, 39 h, 72%; (iii) PCl_5, CH_2Cl_2, 0 °C, 1 h; (iv) $AlCl_3$, CH_2Cl_2, 0 °C, 90 m; (v) $NaBH_4$, MeOH, THF, 2 h; (vi) TsOH, benzene, reflux, 2 h, 6% from **19**; (vii) BBr_3, CH_2Cl_2, 2 h, 80%.



Scheme 4. Reagents and conditions: (i) PCl_5, CH_2Cl_2, 0 °C, 75 m; (ii) $AlCl_3$, CH_2Cl_2, 0 °C, 75 m; (iii) MeMgCl, THF, 90 m; (iv) TsOH, benzene, reflux, 2 h, 6% from **14**; (v) BBr_3, CH_2Cl_2, 2 h, 53%.

dibromoxylene **25** under phase transfer conditions afforded the parent spiroindene **26** in low yield. Similarly, reaction of **24** with dibromide **27**[12] under the same conditions resulted in spiro-alkylation with deprotection to afford the hydroxy-spiroindene **28** in very low yield. Not surprisingly, **26** and **28** were significantly less active than **10**.

Although the overall yield of the spiroalkylation route was disappointing in the examples outlined in Scheme 5, we decided to try to apply it to the synthesis of **11** and the isomeric spiroindene **35** with the hope that we could optimize the yield of the problematic spiro-alkylation. LAH reduction of the known indanone **29**[13] followed by dehydration of the resulting alcohol with *p*-toluenesulfonic acid afforded a mixture of the isomeric 2-phenylindenes **31** and **32**. Since deprotonation of **31** or **32** affords the same indenyl anion, no attempt was made to separate the two isomers. Alkylation of **31**/**32** with dibromide **25** afforded the expected mixture of spiroindenes **21** and **33** in very low yield.[14] Deprotection of **33** afforded the spiroindene diol **34**. Diol **34** was less active than **10** but was comparable to the isomeric diol **11**. The low overall yield of **34** combined with the una-

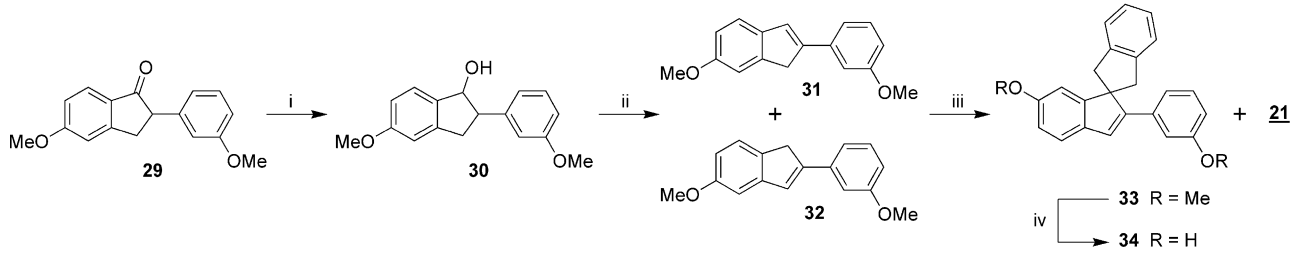


Scheme 5. Reagents and conditions: (i) THF, 50% aq NaOH, $PhCH_2N(CH_3)_4Cl$, 22 h, 50 °C, 16%; (ii) THF, 50% aq NaOH, $PhCH_2N(CH_3)_4Cl$, 23 h, 50 °C, 5%.

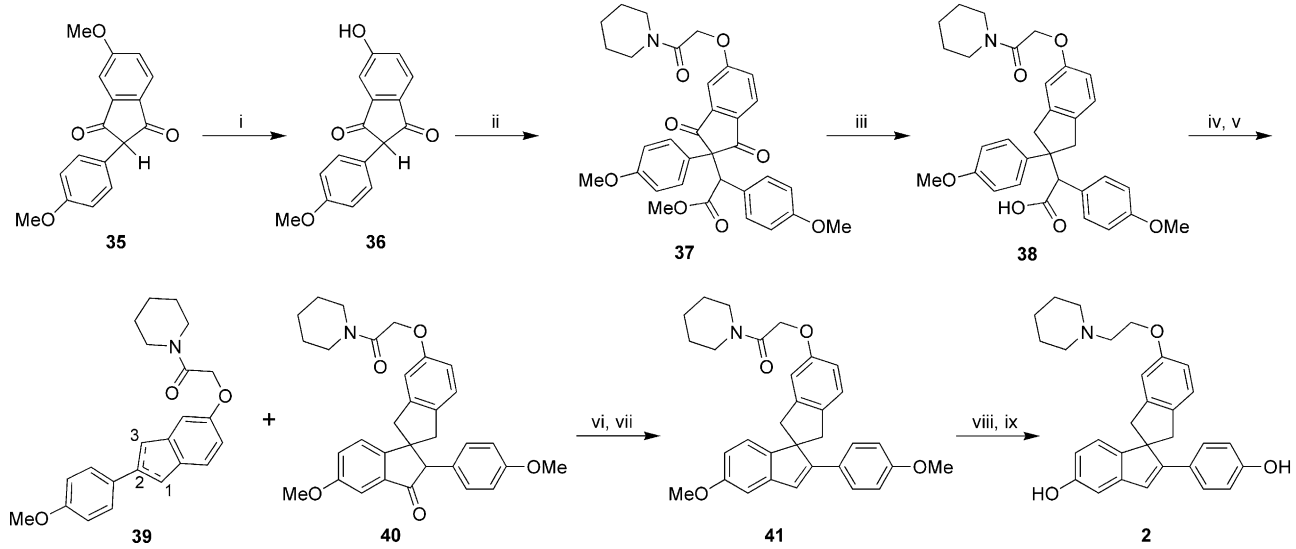
voidable production of two isomeric spiroindenes prompted us to abandon this route (Scheme 6).[15]

The disappointing results obtained with the spiro-alkylation sequence prompted us to return to the original sequence for the synthesis of the fully elaborated spiroindene **2** (Scheme 7). Selective deprotection of the known anisindione derivative **35**[16] with sodium thiomethoxide under an argon atmosphere[17] afforded the desired phenol **36** in good yield. A one-pot selective alkylation of **36** at the indandione carbon with bromide **12** followed by alkylation of the phenol with N-chloroacetyl-piperidine[18] provided the advanced intermediate **37** in very good yield. As expected, catalytic hydrogenation of **37** reduced the ketones and hydrolyzed the methyl ester to afford acid **38** in good yield. The acid chloride was formed by reaction of **38** with PCl_5 and treated in situ with $AlCl_3$ to effect cyclization to the ketone **40** in 24% yield. This cyclization reaction was plagued by a fragmentation reaction that afforded by-product **39** in 50% yield as a mixture of olefin isomers. To date, we have been unable to find conditions which avoid this undesirable side reaction.

Cyclic ketone **40** was reduced with $NaBH_4$ and the resulting alcohol was treated with toluenesulfonic acid to effect elimination to the olefin **41**. Reduction of the amide with LAH proceeded smoothly to afford the tertiary amine. However, deprotection of the methyl ethers proved to be problematic. The yield of the desired spiro-



Scheme 6. Reagents and conditions: (i) $LiAlH_4$, THF, 86%; (ii) TsOH, benzene, reflux, 22%; (iii) **25**, THF, 50% aq NaOH, $PhCH_2N(CH_3)_4Cl$, 54 h, 50 °C, 35% combined yield of **21** and **33**; (iv) NaSMe, DMF, 100 °C, 22 h, 5% from **31**/**32**.



Scheme 7. Reagents and conditions: (i) NaSMe, NaHCO3, DMF, 130 °C, Ar atmosphere, 58%; (ii) **12**, $NaHCO_3$, DMF, 25 °C, 2 h, then N-chloroacetyl-piperidine, K_2CO_3, 55 °C, 3 h, 83%; (iii) H_2, $Pd(OH)_2/C$, EtOAc, EtOH, AcOH, 69 h, 78%; (iv) PCl_5, CH_2Cl_2, 0 °C; (v) $AlCl_3$, CH_2Cl_2, 0 °C, 24% (also isolated 50% yield of **39** as a mixture of 1,2- and 2,3- olefin isomers); (vi) $NaBH_4$, THF; (vii) TsOH, benzene, reflux, 52%; (viii) $LiAlH_4$, THF; (ix) BBr_3, CH_2Cl_2, 4%.

indene **2** was very low due to the formation of several rearrangement products. However, it was possible to isolate sufficient quantities of **2** for biological evaluation. We were pleased to find that **2** is an extremely potent estrogen receptor ligand, perhaps slightly more potent than raloxifene.

It is clear from the data in Table 1 that the 2-phenylspiroindenes can bind very efficiently to human estrogen receptors. The binding data for the rat and human receptors generally parallel each other with the exception of the methyl-indene analogue **23** which appears to be significantly more potent in the rat. The most active compound, **2**, has binding affinity that is comparable to, or perhaps slightly better than, raloxifene (**1**) itself. Even the less complex analogues such as **3**, **10**, and **11** are potent estrogen receptor ligands. The binding data confirm the anticipated importance of the position of the phenolic hydroxyl groups. The most active compounds, **2** and **10**, have hydroxyl groups in the same orientation as in **1**. The next most active compounds, **3** and **11**, have the A-ring hydroxyl in the same position as in **1** but either lack the pendant ring hydroxyl, as in **3**, or have it shifted over one carbon, as in **11**. Shifting both hydroxyl groups, as in **34**, results in a further decrease in binding activity. The parent compound, **28**, which lacks both hydroxyl groups, is essentially inactive. Incorporation of the raloxifene side chain into compound **10**, as in analogue **2**, results in only a slight increase in binding affinity. Addition of a methyl group at C-3 of **10**, as in **23**, results in only a slight decrease in binding suggesting that there may be room at this position for small substituents. Further results in this area will be reported in future communications from this laboratory.

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15. Similar results were obtained when this sequence was applied to the synthesis of **16** and its isomer (corresponding to **33**). In this case, the yield of the spiro-alkylation reaction was so low that deprotection of the product was not attempted and the sequence was not completed.
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