Salicylaldoxime Moiety as a Phenolic "A-Ring" Substitute in Estrogen Receptor Ligands

Filippo Minutolo,[‡] Simone Bertini,[‡] Chiara Papi,[‡] Kathryn E. Carlson,[§] John A. Katzenellenbogen,[§] and Marco Macchia*,[‡]

Dipartimento di Scienze Farmaceutiche, Università di Pisa, Via Bonanno 6, 56126 Pisa, Italy, and Department of Chemistry, University of Illinois, 600 S. Mathews Avenue, Urbana, Illinois 61801

Received June 11, 2001

The phenolic "A-ring" of natural and synthetic estrogen receptor (ER) ligands was effectively replaced by a planar six-member ring formed through an intramolecular hydrogen bond within a salicylaldoxime. Thus, oxime **1**, a structural analogue of a triarylethylene estrogen, showed a significant binding affinity for the ER. The OH of the oxime function appears to mimic the phenolic OH present in more "classical" ER ligands because the binding reduced when the oxime OH is methylated (**2**) or absent (**3**).

Introduction

Estrogens are hormones that play important roles in regulating the development and function of reproductive tissues, and they have significant effects on a wide variety of other tissues, such as bone, the cardiovascular and central nervous systems, and the liver.[1] The effects of estrogens are mediated by a specific receptor, which functions as a ligand-inducible nuclear transcription factor.[2] Two subtypes of the estrogen receptor, ERα and ERβ, have been described.[3,4] Although it is not clear what roles ERα and ERβ play in the various physiological effects of estrogens, these ER subtypes have different tissue distributions, and, in some cases, they show considerable differences in their response to certain receptor ligands.[5−7] ER is also involved in several diseases, such as breast and endometrial cancer, prostate hypertrophy, and osteoporosis;[8] for this reason, some ER ligands that possess partial antagonist properties, like tamoxifen and raloxifene, have proven to be effective in the treatment or prevention of these diseases.[9]

One intriguing aspect of the pharmacology of estrogens is that they demonstrate remarkable patterns of selectivity. Some estrogens, particularly those of the newly designated class of selective estrogen receptor modulators, or SERMs, are able to stimulate estrogenic actions in those tissues where they are desired, such as the bone, liver, and cardiovascular system but are inactive or block estrogen action at other sites where stimulation might be undesirable, such as the breast and uterus.[5,9] The search for SERMs that would have an ideal profile of tissue selectivity for menopausal hormone replacement or for the prevention or treatment of breast cancer is an active aspect of current pharmaceutical and academic research endeavors.[5,9]

While the mechanistic basis of the tissue-selective pharmacology of estrogens is not well understood, it has been proposed to result either from selective action through the two ER subtypes, ERα and ERβ,[3,5] or from differential interactions that an ER-hormone complex might have with the different constellation of coregulatory proteins or effector components that are present within the cells of different tissues and at different gene regulatory sites.[1] Regardless of the underlying mechanism, however, it is the structure of the ER ligand that plays the critical determining role in the pharmacological character of estrogens. This has led to a search for estrogens having novel structures and thereby, potentially, novel pharmacology.

The classes of nonsteroidal ER ligands known so far embody a remarkably heterogeneous variety of molecular structures.[10−12] Nevertheless, the striking chemical feature common to nearly all synthetic ER ligands possessing a good binding affinity is the presence of a phenolic ring that seems to mimic the steroid "A-ring" present in natural estrogens. This phenolic group is thought to be responsible for the strongest attractive polar interaction between ligand and receptor, through the formation of a hydrogen bond network that includes a bound water molecule and two amino acid residues of the ER ligand binding domain (Glu353 and Arg394).[13,14] In connection with our ongoing interest in discovering new classes of chemical structures that possess good estrogen receptor binding affinity with potential SERM activity,[6,7] we have investigated an unprecedented bioisosteric replacement of the phenolic A-ring.

The typical estrogen ligand pharmacophore model[12] (Figure 1, left) contains a generic and quite variable core structure bearing one phenolic ring (A) and a second aromatic substituent which can be differently substituted (R). In addition, this generalized ligand structure typically tolerates (or, in fact, may prefer) the presence of one or two additional substituents, one of which may be another aromatic group. An example of a typical nonsteroidal estrogen that conforms to this pharmacophore model are the diarylnaphthalene systems shown in the middle of Figure 1. Such systems, and their B-ring dihydro- and tetrahydro-analogues, are well represented in the nafoxidine class of antiestrogens.[15]

We envisaged the possibility that 3,4-disubstituted salicylaldoxime derivatives (Figure 1, right) might be

* Correspondence and reprints: e-mail, mmacchia@farm.unipi.it; tel, +39-050-500209; fax, +39-050-40517.
[‡] Università di Pisa.
[§] University of Illinois.

10.1021/jm010948j CCC: $20.00
Published on Web 10/06/2001

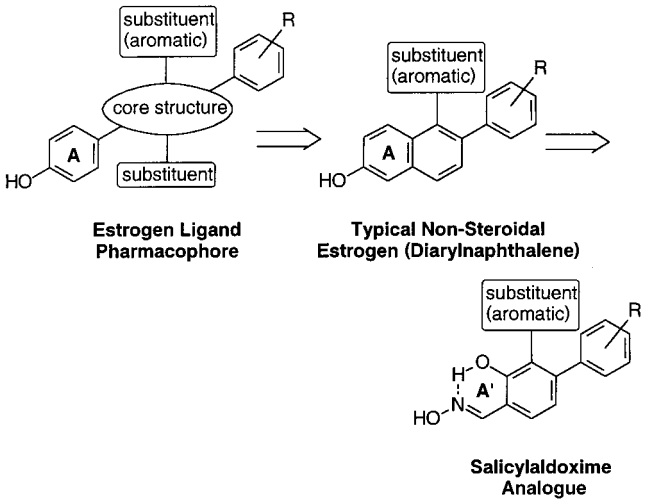
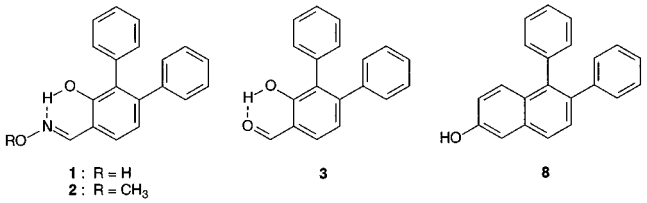


Figure 1. Structural relatedness of salicylaldoxime (bottom) and diarylnaphthalene (center) analogues with the estrogen ligand pharmacophore model (left).

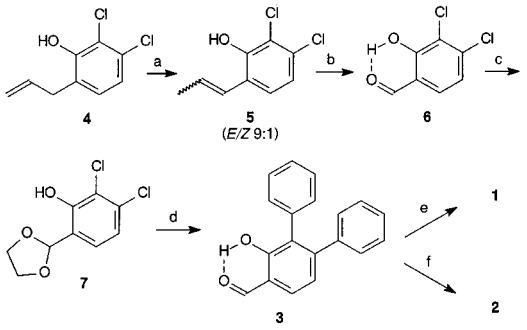
good estrogen receptor ligands because they possess a hydroxy-substituted six-membered pseudo-ring (A′), formed by an intramolecular hydrogen bond present in a salicylaldoxime moiety. The existence of this hydrogen bond can be verified by IR and NMR experiments, and it confirms that the oxime in this system has the (*E*)-geometry.[16]

This ring (A′) presents several features that indicate its similarity with the phenolic A-ring: (*i*) both rings have approximately same size and same planar π-conjugated (at least partially, in the case of the salicylaldoximes) hexagonal geometry; (*ii*) the OH of the oxime group is attached to an sp^2 hybridized atom (nitrogen) that is intramolecularly hydrogen-bonded to the ortho phenol and has a pK_a value around 10, within the pK_a range of typical phenolic OH groups; (*iii*) the position of the oxime OH group corresponds to the position 3 of the phenolic A ring, i.e., the position actually occupied by an OH in classical ER ligands. Moreover, salicylaldoximes have an aromatic ring that can act as the "core structure" carrying additional substituents, at least one of which should be an aromatic group. The structural similarity of the salicylaldoxime to the phenol is further supported by the ligand molecular modeling presented below.

We began our investigation with 3,4-diaryl-substituted salicylaldoximes since they closely resemble the diarylnaphthalenes, a chemical motif that includes many good ligands for the ER.[15] In this paper we report the synthesis, molecular modeling, and an evaluation of the ER receptor binding affinity properties of 3,4-diphenylsalicylaldoxime **1**, its *O*-methyl analogue **2**, and their aldehyde precursor **3**, as well as that of a diarylnaphthalene compound (**8**),[17] a nonsteroidal estrogen that is isosteric with salicylaldoxime **1**.



Scheme 1[a]



[a] Key: (a) *t*-BuOK, DMSO, 55 °C, 3 h; (b) OsO_4 (0.4 mol %), $NaIO_4$ (2.3 equiv), dioxane−H_2O (1:1), rt, 30 min; (c) $(CH_2OH)_2$, *p*-TsOH (cat.), dry benzene, reflux, Dean−Stark trap; (d) 2 times: $Pd_2(dba)_3$ (3.2 mol %), Cy_3P (8.3 mol %), $PhB(OH)_2$ (1.5 equiv), Cs_2CO_3 (1.7 equiv), dioxane, 80 °C, 16 h; (e) NH_2OH·HCl, MeOH−H_2O (10:1), 50 °C, 2 h; (f) NH_2OCH_3·HCl, EtOH−H_2O (10:1), 50 °C, 15 min.

Results and Discussion

Chemical Synthesis. The synthesis of compounds **1**−**3** was accomplished as shown in Scheme 1, starting from 2,3-dichloro-6-allylphenol **4**, which was prepared from commercially available 2,3-dichlorophenol as previously reported.[18] Rearrangement of the terminal double bond of **4** to an internal, conjugated position was achieved by treatment with potassium *t*-butoxide in DMSO;[19] the product, compound **5**, consisted of a 9:1 mixture *E*/*Z* isomers. Salicylaldehyde **6** was obtained by oxidative cleavage of the double bond present in **5** (*E*/*Z* mixture), using sodium periodate and catalytic amounts of osmium tetroxide.[20] The aldehyde was then protected as a cyclic acetal with ethylene glycol[21] to obtain compound **7**.

This dichloride **7** was then submitted to two identical, sequential Pd-catalyzed cross-coupling steps with phenylboronic acid (1.5 equiv each step). It is known that typical Suzuki conditions are suitable for aryl bromides and iodides, but they are inefficient for cross-coupling reactions of aryl chlorides.[22] However, aryl chlorides do react well under appropriate conditions, using $Pd_2(dba)_3$ as the catalyst, a trialkylphosphine as the ligand, Cs_2CO_3 as the base, and dioxane as the solvent.[23] In fact, under these conditions, dichloride **7** gave reasonable yields of the diphenyl-substituted product **3**. It should be noted that under these conditions, the acetal protecting group is cleaved, giving the free aldehyde **3**. Nevertheless, we determined that protection of the aldehyde is important; otherwise, the yields of the two cross-coupling steps decline significantly. The free salicylaldehyde probably acts as a bidentate chelate that competes with other ligands for the metal centers (palladium or boron) during the Suzuki coupling reactions. We have also tried to effect a double substitution of the two phenyl groups in one step, by using 3 equiv or more of phenylboronic acid at one time. This approach, however, resulted in the formation of considerable quantities of biphenyl, a self-coupling product of phenylboronic acid, together with only very low amounts of the desired di-adduct. Therefore, the sequential sequence, using 1.5 equiv of phenylboronic acid each step, turned out to be the best way that we found to obtain compound **3**.

Table 1. Relative Binding Affinities[a] of Salicylaldehyde-Related Compounds **1**−**3** and Reference Compound **8** for the Estrogen Receptors α and *β*

ligand	uterine ER	hERα	hER*β*
estradiol	(100)	(100)	(100)
1	0.85 ± 0.21	1.13 ± 0.18	1.71 ± 0.42
2	<0.010	0.012 ± 0.001	0.013 ± 0.003
3	<0.010	0.0084 ± 0.001	0.0080 ± 0.003
8	27.7 ± 3.6	116 ± 23	74.4 ± 20.9

[a] Determined by a competitive radiometric binding assay with [^{3}H]estradiol. Cytosol preparations of lamb uterus or full-length human ERα and ER*β* (PanVera) were used.[24,25] Values are reported as the mean ± SD under these conditions. The K_d for estradiol in all three receptor preparations is 0.3 nM.

Salicylaldoxime **1** was obtained by treating aldehyde **3** with hydroxylamine hydrochloride. Analogously, *O*-methyl salicylaldoxime **2** was obtained by condensation of **3** with methoxylamine hydrochloride. In both cases (**1** and **2**), the (*E*)-form of the oxime was the only diastereoisomer formed, presumably, because the intramolecular hydrogen bond, which can only form in the (*E*)-isomer, contributes to the oxime stability. A confirmation of the (*E*)-configuration of the oxime moiety was evident from the chemical shift value of the oxime proton, which is found well below 8 ppm (8.31 ppm for **1** and 8.24 ppm for **2**). Such a downfield value is typical for aromatic oximes possessing an (*E*)-configuration, whereas the same group with a (*Z*)-configuration is usually reported between 7.3−7.6 ppm. This is due to the fact that when the oxime proton is on the same side and in a close spatial contact with an electronegative heteroatom such as an oxygen atom ((*E*)-configuration of the oxime), it is deshielded to a greater extent than when it is positioned on the other side ((*Z*)-configuration).[24]

Estrogen Receptor Binding Assays. The binding affinity of the new estrogen mimic **1** and its two analogues **2** and **3**, as well as the reference estrogen **8**, for both estrogen receptor subtypes, ERα and ER*β*, was determined in a radiometric competitive binding assay, using methods that we have described elsewhere in detail.[25,26] In Table 1, we report the relative binding affinity (RBA) values for these compounds, determined in a uterine cytosol ER preparation, as well as with purified full-length human ERα and ER*β*; these binding affinity values are reported relative to estradiol, which is set at 100%.

Of the salicylaldehyde compounds we prepared, we expected that the oxime **1** was most likely to be a good ligand, because only it possesses an OH group that might mimic the phenolic OH group present in the A-ring of natural and synthetic ER-ligands (cf. Figure 1). On the other hand, we also wanted to verify the effect of removing this oxime OH group, either by its methylation, as in compound **2**, or by its absence, as in compound **3**.

From the results shown in Table 1, it is evident that oxime **1** is an effective ligand for the estrogen receptor in all three preparations, having RBA values in the range of ca. 1−2% that of estradiol. It shows no significant difference in its affinity for ERα or ER*β*.

Compared to the affinity of the diarylnaphthalene structural reference compound **8**, oxime **1** has an affinity that is from 30 to 100-fold less. Thus, its K_d value for these estrogen receptors can be estimated to be 10−30 nM, vs 0.3 nM for estradiol. This places the binding affinity of the salicylaldoxime estrogen mimic **1** on a par with that of tamoxifen, as well as that of many other estrogens and antiestrogens.[11] The affinity of oxime **1** is, in fact, rather high for a compound that does not have a phenolic function, and it is comparable to that of many estrogens that do have phenols.[27]

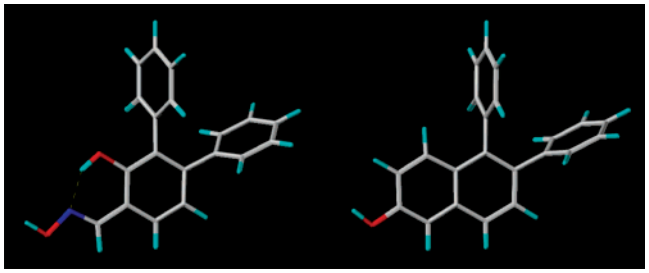


Figure 2. Left: oxime **1**. Right: naphthol **8**. The dihedral angles for the two phenyl groups, listing first the proximal and then the distal one, are: oxime **1**, 69° and 68°; naphthol **8**, 83° and 80°. These structures were obtained by molecular mechanics minimization with the MMFF94 force field within SYBYL 6.7, using the conjugate gradient minimizer to a gradient of 0.05 kcal/(mol Å).

The importance of the oxime OH group in compound **1** is evident from the considerable reduction in the RBA values that was experienced when this group is methylated, as in **2**. In fact *O*-methylated oxime **2** showed a ER binding affinity ca. 100-fold lower than "free" oxime **1**, depending on the receptor preparation. An even more dramatic reduction in binding affinity is shown by salicylaldehyde **3**. This compound possesses the same carbon skeleton as **1** and **2**, but it completely lacks the oxime function. In this case the relative binding affinity values are 150−300 times lower than the ones found with salicylaldoxime **1**. Neither compound **2** nor **3** showed any appreciable ERα/*β* selectivity.

The salicylaldoxime group appears to be an effective mimic of a phenol in the context that we have studied here, that of the estrogen receptor and its ligands. Nevertheless, the binding affinity of the oxime mimic **1** is still 30−100 fold less than that of the structurally congruent phenol **8**. This raises the interesting question whether the lower affinity of compound **1** results from a *specific structural or electronic deficiency* in precisely how the pseudocyclic salicylaldoxime group is mimicking the phenol or from a more *general difference* between ligand **1** and ligand **8**.

Molecular Modeling. To confirm the structural similarity of salicylaldoxime **1** with the reference naphthol **8**, we have subjected both compounds to molecular mechanics minimization.

Comparison of the minimized structures (Figure 2) shows that they are very similar, with the salicylaldoxime system providing a nice structural mimic for the phenol and the two phenyl substituents having very similar dihedral angles (see Figure 2 legend). The slightly smaller dihedral angles in the oxime **1** (69° and 68° vs 83° and 80° for the naphthol **8**) suggest that the oxygen lone pairs in the oxime provide less nonbonded repulsion of the proximal phenyl than does the C−H bond in the naphthol. It seems unlikely that these small differences in dihedral angles are responsible for the difference in binding affinity of the two compounds (see Table 1), but is it of note that the lower affinity oxime

is more planar than is the naphthol. In some related ligands it is thought that ligand "thickness" in this portion of the receptor contributes to high affinity binding.[28,29]

Conclusion

In this investigation we demonstrate that the six-member ring formed by the intramolecular hydrogen bond in the salicylaldoxime **1** appears to be an effective stereoelectronic replacement of the aromatic A-ring of typical estrogen ligands and that the hydroxyl group of the oxime in compound **1** seems to effectively mimic the fundamental role played by the hydroxyl of the phenolic A-ring in the interaction with the estrogen receptor. It is not difficult to see that salicylaldoxime **1** represents the first and simplest member of what might prove to be a large class of novel estrogen receptor ligands, other members of which could be accessed by modifying the aromatic substituents in positions 3 and 4. Investigations along these lines are underway.

Supporting Information Available: Characterization data of compounds **1**−**3** and **5**−**7** and experimental details. This material is available free of charge via the internet at http://pubs.acs.org.

References

(1) Katzenellenbogen, J. A.; O'Malley, B. W.; Katzenellenbogen, B. S. Tripartite Steroid Hormone Receptor Pharmacology: Interaction with Multiple Effector Sites as a Basis for the Cell- and Promoter-Specific Action of These Hormones. *Mol. Endocrinol.* **1996**, *10*, 119−131.

(2) Katzenellenbogen, J. A.; Katzenellenbogen, B. S. Nuclear hormone receptors: ligand-activated regulators of transcription and diverse cell responses. *Chem. Biol.* **1996**, *3*, 529−536.

(3) Mosselman, S.; Polman, J.; Dijekema, R. ERβ: Identification and characterization of a novel human estrogen receptor. *FEBS Lett.* **1996**, *392*, 49−53.

(4) Kuiper, G. G. J. M.; Enmark, E.; Pelto-Huikko, M.; Nilsson, S.; Gustafsson, J. Å. Cloning of a novel receptor expressed in rat prostate and ovary. *Proc. Natl Acad. Sci. U.S.A.* **1996**, *93*, 5925−5930.

(5) Kuiper, G. G. J. M.; Carlsson, B.; Grandien, K.; Enmark, E.; Haggblad, J.; Nilsson, S.; Gustafsson, J. Å. Comparison of the ligand binding specificity and transcript tissue distribution of estrogen receptors alpha and beta. *Endocrinology* **1997**, *138*, 863−870.

(6) Meyers, M. J.; Sun, J.; Carlson, K. E.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. Estrogen receptor subtype-selective ligands: asymmetric synthesis and biological evaluation of *cis*- and *trans*-5,11-dialkyl-5,6,11,12-tetrahydrochrysenes. *J. Med. Chem.* **1999**, *42*, 2456−2468.

(7) Stauffer, S. R.; Coletta, C. J.; Tedesco, R.; Nishiguchi, G.; Carlson, K.; Sun, J.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. Pyrazole Ligands: Structure-Affinity/Activity Relationships and Estrogen Receptor-α-Selective Agonists. *J. Med. Chem.* **2000**, *43*, 4934−4947.

(8) Gustafsson, J. Å.; Kuiper, G. G. J. M.; Enmark, E.; Treuter, E.; Rafter, J. Receptor-Mediated Toxicity. *Arch. Toxicol.* **1998**, *20*, 21−28.

(9) Grese, T. A.; Dodge, J. A. Selective estrogen receptor modulators (SERMs). *Curr. Pharm. Des.* **1998**, *4*, 71−92.

(10) Magarian, R. A.; Overacre, L. B.; Singh, S.; Meyer, K. L. The Medicinal chemistry of nonsteroidal antiestrogens: a review. *Curr. Med. Chem.* **1994**, *1*, 61−104.

(11) Gao, H.; Katzenellenbogen, J. A.; Garg, R.; Hansch, C. Comparative QSAR Analysis of Estrogen Receptor Ligands. *Chem. Rev.* **1999**, *99*, 723−744.

(12) Fink, B. E.; Mortensen, D. S.; Stauffer, S. R.; Aron, Z. A.; Katzenellenbogen, J. A. Novel structural templates for estrogen-receptor ligands and prospects for combinatorial synthesis of estrogens. *Chem. Biol.* **1999**, *6*, 205−219.

(13) Brzozowski, A. M.; Pike, A. C. W.; Dauter, Z.; Hubbard, R. E.; Bonn, T.; Engström, O.; Öhman, L.; Greene, G. L.; Gustafsson, J.-Å.; Carlquist, M. Molecular basis of agonism and antagonism in the oestrogen receptor. *Nature* **1997**, *389*, 753−758.

(14) Oostenbrink, B. C.; Pitera, J. W.; van Lipzig, M. M. H.; Meerman, J. H. N.; van Gunsteren, W. F. Simulations of the Estrogen Receptor Ligand-Binding Domain: Affinity of Natural Ligands and Xenoestrogens. *J. Med. Chem.* **2000**, *43*, 4594−4605.

(15) Lednicer, D.; Lyster, S. C.; Aspergren, B. D.; Duncan, G. W. Mammalian Antifertility Agents. III. 1-Aryl-2-phenyl-1,2,3,4-tetrahydro-1-naphthols, 1-Aryl-2-phenyl-3,4-dihydronaphthalenes, and Their Derivatives. *J. Med. Chem.* **1966**, *9*, 172−176.

(16) Vuik, C. P. J.; ul Hasan, M.; Holloway, C. E. Carbon-13 T_1 Study of Aldehydes and Aldehyde Oximes. *J. Chem. Soc., Perkin 2* **1979**, 1214−1218 and references therein.

(17) Photochemical preparation of compound **8** had been previously described in: Zimmerman, H. E.; Lamers, P. H. Photochemistry of Some Extended π-Systems: Type A and Aryl Rearrangements of Systems with Extended Conjugation Related to Cyclohexadienones and Cyclohexenones. Mechanistic and Exploratory Organic Photochemistry. *J. Org. Chem.* **1989**, *54*, 5788−5804. We found it more convenient to prepare compound **8** by DDQ-aromatization followed by BBr_3-demethylation of 1,2-diphenyl-6-methoxy-3,4-dihydronaphthalene, reported in ref 15.

(18) Hoffman, W. F.; Woltersdorf, O. W.; Novello, F. C.; Cragoe, E. J., Jr.; Spinger, J. P.; Sherman Watson, L.; Fanelli, G. M., Jr. Acylaryloxyacetic Acid Diuretics. 3. 2,3-Dihydro-5-acyl-2-benzofurancarboxylic Acids, a New Class of Uricosuric Diuretics. *J. Med. Chem.* **1981**, *24*, 865−873.

(19) Guillaumet, G.; Hretani, M.; Coudert, G. Synthèse de dioxinocoumarines angulaires. *J. Heterocycl. Chem.* **1989**, *26*, 193−197.

(20) Demuth, M.; Ritterskamp, P.; Weigt, E.; Schaffner, K. Total Synthesis of (−)-Coriolin. *J. Am. Chem. Soc.* **1986**, *108*, 4149−4154. Note: we found that yields are considerably improved by using at least 2.3 equiv of sodium periodate, since 1 equiv is consummated for the initial osmium-catalyzed dihydroxylation, and another equivalent is needed for the oxidative cleavage of the C−C bond of the diol formed in the first step.

(21) Crimmins, M. T.; DeLoach, J. A. Intramolecular Photocycloadditions-Cyclobutene Fragmentation: Total Synthesis of (±)-Pentalene, (±)-Pentalenic Acid, and (±)-Deoxypentalenic Acid. *J. Am. Chem. Soc.* **1986**, *108*, 800−806.

(22) Miyaura, N.; Suzuki A. Palladium-Catalyzed Cross-Coupling Reactions of Organoboron Compounds. *Chem. Rev.* **1995**, *95*, 2457−2483.

(23) Littke, A. F.; Fu, G. C. A Convenient and General Method for Pd-Catalyzed Suzuki Cross-Coupling of Aryl Chlorides and Arylboronic Acids. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3387−3388.

(24) Karabatsos, G. J.; Hsi, N. Structural Studies by Nuclear Magnetic Resonance-XI: Conformations and Configurations of Oxime *O*-Methyl Ethers. *Tetrahedron* **1967**, *23*, 1079−1095.

(25) Katzenellenbogen, J. A.; Johnson, H. J., Jr.; Myers, H. N. Photoaffinity Labels for Estrogen Binding Proteins of Rat Uterus. *Biochemistry* **1973**, *12*, 4085−4092.

(26) Carlson, K. E.; Choi, I.; Gee, A.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. Altered Ligand Binding Properties and Enhanced Stability of a Constitutively Active Estrogen Receptor: Evidence That an Open-Pocket Conformation is Required for Ligand Interaction. *Biochemistry* **1997**, *36*, 14897−14905.

(27) Anstead G. M.; Carlson, K. E.; Katzenellenbogen J. A. The Estradiol Pharmacophore: ligand structure-estrogen receptor binding affinity relationships and a model for the receptor binding site. *Steroids* **1997**, *62*, 268−303.

(28) Hwang, K. J.; Carlson, K. E.; Anstead, G. M.; Katzenellenbogen, J. A. Donor−Acceptor Tetrahydrochrysenes, Inherently Fluorescent, High Affinity Ligands for the Estrogen Receptor: Binding and Fluorescence Characteristics, and Fluorometric Assay for Receptor. *Biochemistry* **1992**, *31*, 11536−11545.

(29) Hwang, K. J.; O'Neil, J. P.; Katzenellenbogen, J. A. 5, 6, 11, 12-Tetrahydrochrysenes: Synthesis of Rigid Stilbene Systems Designed to be Fluorescent Ligands for the Estrogen Receptor. *J. Org. Chem.* **1992**, *57*, 1262−1271.

JM010948J