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Benzopyrans as selective estrogen receptor β agonists (SERBAs). Part 3: Synthesis of cyclopentanone and cyclohexanone intermediates for C-ring modification

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Abstract—Benzopyrans are selective estrogen receptor (ER) β agonists (SERBAs), which bind the ER subtypes α and β in opposite orientations. Here we describe the syntheses of cyclopentanone and cyclohexanone intermediates for SAR studies of the C-ring on the benzopyran scaffold. Modification of the C-ring disrupts binding to ERα, thus improving ERβ selectivity up to 100-fold. X-ray cocrystal structures confirm previously observed binding modes.

The estrogen receptors are members of the steroid nuclear hormone receptor family. ERα is important for development and regulation of the female reproductive system as well as maintenance of the skeletal and cardiovascular systems. ERβ was discovered in 1996 in the rat prostate gland and adds another layer of complexity to our understanding of estrogen physiology.[1] While ERα is expressed in nearly all tissues of both sexes, ERβ is expressed in the ovaries, uterus, and oviduct of the female reproductive tract but not in breast tissue; while in males, ERβ is expressed in the prostate and epididymis but not in the testes.[2] Selective ER modulators (SERMs) demonstrate tissue type functional selectivity with agonist activity in bone, liver, and cardiovascular tissues, and antagonist activity in the uterus and breast.[3] This tissue type functional selectivity is most likely due to the interaction of ligand bound receptor with coactivators that combine to form gene transcription complexes or interaction with corepressors that inhibit gene transcription.

Over the last decade several groups have reported ERβ selective ligands.[4] Our own efforts focused on the benzopyran scaffold resulting in the development of benzopyran **1a** as a selective estrogen receptor β agonist (SERBA-1).[5] Recently we reported structure activity relationship (SAR) studies focused on the size of the 3,4-fused ring labeled C in Figure 1.[6] The addition of a fused cyclopentane ring at the 3,4-carbon positions of the benzopyran scaffold resulted in a dramatic increase in binding affinity, 9-fold selectivity for ERβ over ERα, and provided us with a ligand architecture containing structural elements that take advantage of the space available above and below the plane marked by the two phenol rings. As can be seen in Figure 1, the cyclopropane is projected down from the plane marked

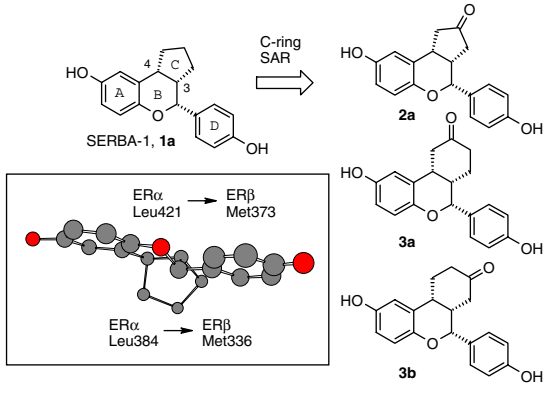

Figure 1. Unique structural features of the benzopyran platform.

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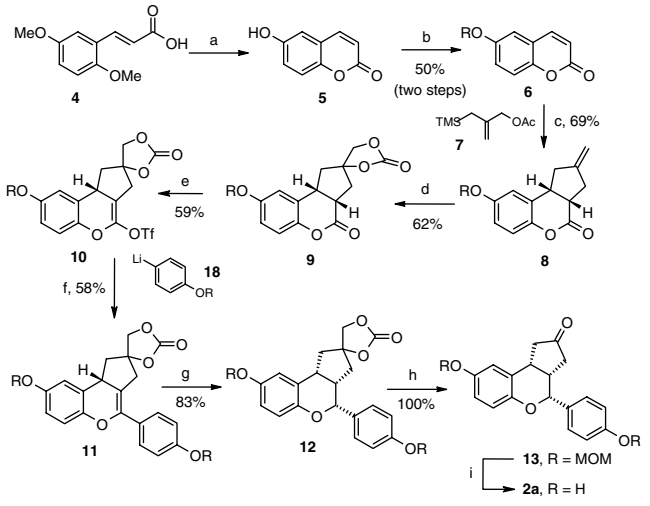
by the phenol rings. This unique structural feature allowed us to take advantage of the Met-421 → Ile-373 and the Leu-384 → Met-336 differences between the binding pockets of ERα → ERβ. Here we describe the syntheses of cyclopentanone **2a** and cyclohexanones **3a** and **3b**. The ketone functional groups of these late stage intermediates served as handles to perform SAR studies of the C-ring on the benzopyran scaffold.

Cyclopentanone **2a** was prepared as described in Scheme 1.[7] Commercially available 2,5-dimethoxycinnamic acid (**4**) was treated with boron tribromide to remove the methyl groups and promote cyclization to 6-hydroxycoumarin (**5**), which was then protected as its MOM-ether to give **6**. The Trost transition metal-catalyzed[8] trimethylenemethane (TMM) cycloaddition[8] was used to install a cyclopentane ring containing an *exo*-methylene group to give lactone **8**. The *exo*-methylene group, which serves as a latent ketone, was dihydroxylated with osmium tetroxide and the resulting diol was protected as its cyclic carbonate using phosgene to give **9**. The lactone **9** was deprotonated with LiHMDS and the resulting lactone enolate was reacted with *N*-phenyl triflamide[9] to give lactone enol triflate **10**. Negishi's palladium-catalyzed coupling[10] conditions were used to couple the lactone enol triflate **10** with the aryl zinc reagent generated from aryl lithium **18** to give the MOM-protected 4-(4*H*-chromen-2-yl)phenol **11**. The enol ether of **11** was easily reduced by hydrogenation over Pd/C to give exclusively the all *cis*-stereoisomer of flavanol analog **12**. At this point the latent ketone could be revealed by hydrolyzing the cyclic carbonate of **12** with LiOH and then cleaving the diol to the ketone with sodium periodate in the same pot. This procedure gave MOM-protected cyclopentanone **13**, which served as a late stage intermediate for the synthesis of C-ring functionalized derivatives of SERBA-1 (**1a**). The MOM-protecting groups of **13** could be removed under mildly acidic aqueous conditions to give cyclopentanone **2a**.

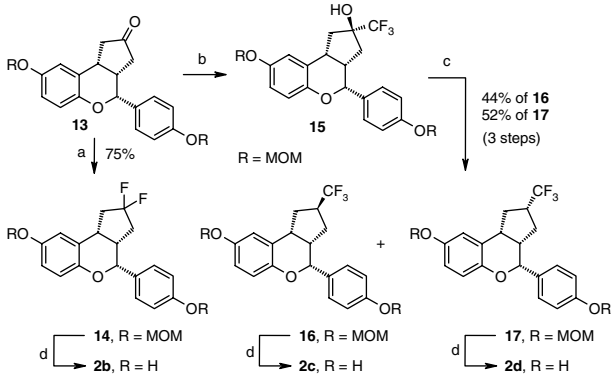


Scheme 1. Coumarin route to cyclopentanone intermediate **13** for C-ring SAR. R = MOM; Reagents and conditions: (a) BBr_3, CH_2Cl_2, rt–82 °C; (b) MOMCl, *i*-Pr_2EtN, CH_3CN; (c) **7**, $Pd(OAc)_2$, $P(OEt)_3$, THF, 60 °C; (d) i—OsO_4, NMO, *t*-BuOH, H_2O, THF; ii—$COCl_2$, Et_3N, CH_2Cl_2, 0 °C; (e) LiHMDS, THF, −78 °C; $PhNTf_2$, HMPA; (f) i—**18**, $ZnCl_2$, THF, 0 °C; ii—**10**, $Pd(PPh_3)_4$, THF, 50 °C; (g) 60 psi H_2, Pd/C, MeOH; (h) LiOH, H_2O, THF; $NaIO_4$; (i) HCl, H_2O, THF.

The use of cyclopentanone **13** as a late stage intermediate for C-ring SAR studies is described in Scheme 2. Treatment of **13** with DAST[11] gave the difluoromethylene derivative **14**, which was deprotected with aqueous HCl to give difluoromethylene cyclopentane **2b**. Ruppert's reagent[12] was added to the ketone of **13** to give trifluoromethyl cyclopentanol **15**. The tertiary alcohol of **15** was removed using Dolan and MacMillan's[13] modified Barton–McCombie[14] radical deoxygenation conditions. The methyl oxalyl ester of **15** was prepared using methyl oxalyl chloride and DMAP, and was then subjected to radical reduction initiated by AIBN and heat in the presence of triphenyl silane. This procedure gave a nearly 1:1 mixture of trifluoromethyl cyclopentane diastereomers **16** and **17**. The diastereomers were easily separated by silica gel chromatography and then deprotected to give the trifluoromethyl cyclopentanes **2c** and **2d**.[15]

We wanted to compare the trifluoromethyl cyclopentane derivatives described in Scheme 2 to the simple methyl analog. This compound was prepared using the reductive cyclization route reported earlier[5] and is described in Scheme 3. The bis-methyl ester of commercially available (+)-3-methylhexanedioic acid (**19**) was prepared using sulfuric acid and methanol. Treatment of **20** with sodium methoxide in methanol and toluene effected a Dieckmann cyclization to give a mixture of the 3- and 4-methyl substituted isomers of methyl 2-oxocyclopentanecarboxylate (**21** and **22**). This mixture could not be separated; however, when treated with triflic anhydride in the presence of Hunig's base, the 4-methyl isomer was preferentially converted to enol triflate **23**, which could be easily purified by silica gel chromatography. Enol triflate **23** was carried through the reductive cyclization route to provide methyl cyclopentane **2e**.

The synthesis route that led to cyclohexanones **3a** and **3b** is described in Scheme 4. The approach to cyclohexanone **3a** utilized a Diels–Alder reaction as the key step to install the C-ring. Beginning with hydroxy-coumarin



Scheme 2. Benzopyrans prepared from ketone intermediate **13**. Reagents and conditions: (a) DAST, $ClCH_2CH_2Cl$, 40 °C; (b) $TMSCF_3$, TBAF, THF; (c) i—$ClCOCOOCH_3$, DMAP, Et_3N, CH_2Cl_2; ii—Ph_3SiH, AIBN, toluene, 80 °C; (d) HCl, H_2O, THF.