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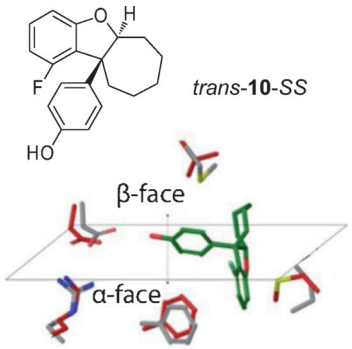
Nothing flat about it: A T-shaped *trans-SS* diastereomer of 4-{3-fluoro-8-oxatricyclo[7.5.0.0^{2,7}]tetradeca-2,4,6-trien-1-yl}-phenol (**10**) was found to be 1000-fold selective for ERβ over ERα. This compound exhibits ~10 nM potency and appears to be the first to take advantage of both conservative amino acid differences found in the α- and β-faces of the binding cavities of ERα and ERβ.



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Design of a Highly Selective and Potent Class of Non-planar Estrogen Receptor β Agonists

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Design of a Highly Selective and Potent Class of Non-planar Estrogen Receptor β Agonists

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Selective activation of the estrogen receptor β (ERβ) could be a safe approach to hormone replacement therapy for both women and men, in contrast to the estrogens currently used for women which activate both ERβ and ERα, occasionally causing severe side effects. The selective ERβ agonist AC-131 has shown efficacy in animal models of Parkinson's disease and neuropathic pain. With the use of AC-131 as template, herein we report the discovery, synthesis, and structure–activity relationship (SAR) study of a new class of dihydrobenzofurans as potent and selective ERβ agonists. The SAR was established by enantioselective synthesis, molecular modeling, and whole-cell-based functional assays. The most potent diastereomer, *cis*-**10**-*SR*, was shown to have an EC_{50} value of <1 nM, potency 100-fold higher than that of AC-131. Even more interestingly, compound *trans*-**10**-*SS* exhibited 1000-fold ERβ/ERα selectivity while still maintaining good potency (~10 nM). In addition, *trans*-**10**-*SS* showed only partial agonist activity (30–60% Eff.) toward ERα at 10 μM. This unprecedented selectivity could be rationalized by molecular modeling. Compound *trans*-**10**-*SS* appears to be the first molecule to take advantage of both conservative amino acid differences found in the α- and β-faces of the binding cavities of ERα and ERβ.

Introduction

Subtype-selective estrogen receptor modulation appears to be important in several pathological processes of neurodegenerative disorders, including Parkinson's disease (PD), Alzheimer's disease (AD), multiple sclerosis, and amyotrophic lateral sclerosis.[1] In most of these diseases, aging is the major risk factor, and the diseases occur around the point in life when bioavailable endogenous sex steroid levels in plasma are generally decreasing.[2] Mechanistically, the protective effects of estrogens have been linked to stabilization of mitochondria by protection against oxidative stress.[3] In addition, estrogens regulate enzymes that catabolize proteins which aggregate in AD and PD, such as insulin-degrading enzyme and cathepsin D, which degrade the Aβ-peptide and α-synuclein, respectively.[4] Furthermore, estrogen signaling plays an essential role in modulating neuroplasticity and cognition.[5]

The therapeutic use of the endogenous estrogen 17β-estradiol (E2) (Figure 1), which potently activates both nuclear ERα and ERβ, is limited by its feminizing effects and an increased risk of cancer.[6] However, these side effects are believed to be associated with activation of ERα. Thus, compounds selective for ERβ could potentially be used safely for chronic treatment in both men and women.

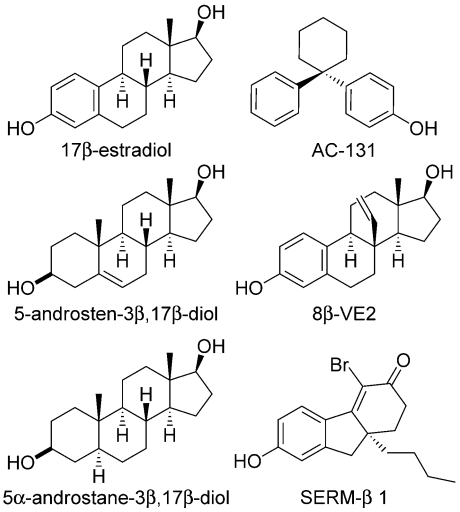

Figure 1. Estrogen receptor agonists.

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In 2008, we reported on a nonsteroidal selective ERβ agonist, AC-131, (Figure 1) and evaluated this molecule in several pain animal models involving nerve injury or sensitization and chronic inflammatory pain.[7] AC-131 alleviated tactile hyperalgesia induced by capsaicin and reversed tactile allodynia caused by spinal nerve ligation and various chemical insults. Moreover, AC-131 did not influence the pain threshold of normal healthy animals. AC-131 was further evaluated in an animal model of PD induced through bilateral 6-hydroxydopamine lesions of the substantia nigra. In this model, AC-131 prevented motor, cognitive, and sensorimotor gating deficits and mitigated the loss of dopamine neurons in the substantia nigra. Interestingly, in male rats, E2 did not show the same neuroprotective benefits as the selective ERβ agonist, AC-131.[1d] Hence, in addition to a beneficial safety profile, a selective ERβ agonist could have a different pharmacological profile from that of the nonselective E2. A further indication of this is the identification of two endogenous ligands, 5-androsten-3β,17β-diol and 5α-andostane-3β,17β-diol, which activate ERβ (Figure 1).[1c]

A common method to make compounds more potent is to increase their rigidity. The two compounds SERM-β 1[8] and 8β-VE2[9] are examples of potent and rigid ERβ-selective agonists. Hence, connecting one of the aryl rings with the cyclohexyl moiety of AC-131 could potentially form at least two rigid tricyclic compounds (Figure 2). Basic molecular modeling indicated that both the benzofuranol and the benzofuran-phenol had reasonable overlays with other non-planar ERβ agonists, implying that both could potentially modulate ERβ. Therefore, both compounds were synthesized. However, biological evaluation showed that only the benzofuran-phenols were active at ERβ. Herein we describe the enantioselective synthesis and biological evaluation, including the establishment of an SAR profile, of a new class of selective ERβ agonists based on a benzofuran-phenol scaffold.

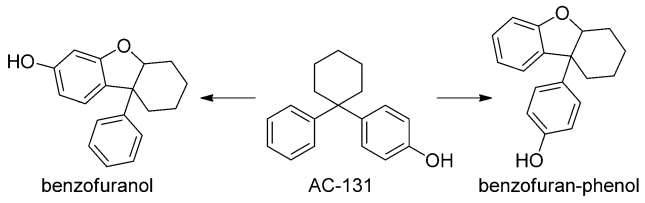
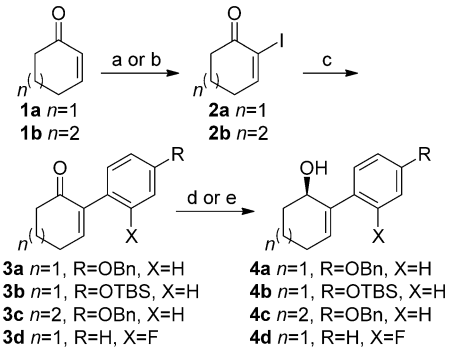


Figure 2. Connection of the cyclohexyl group in AC-131 with one of the aryl moieties generates two different scaffolds: benzofuranol and benzofuran-phenol.

Results and Discussion

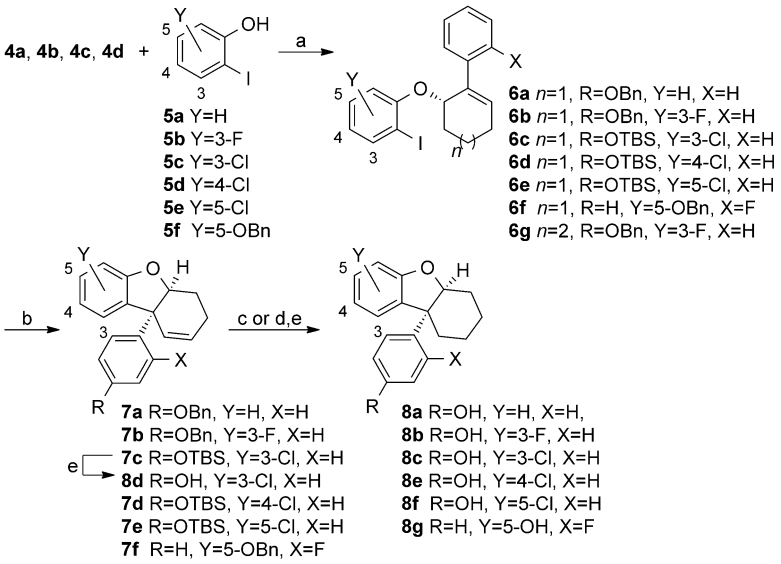
In the development of next-generation ERβ agonists based on AC-131, we envisioned that connecting one of the aryl rings with the cyclohexane, creating two stereogenic centers, would yield a rigid scaffold which, in addition to being more potent and selective, would simplify the establishment of an SAR profile. It was discovered that optically pure dihydrobenzofuran-phenols are potent ERβ agonists (Figure 2). However, the initial synthesis we used was laborious (seven steps), time consuming, and generated isomeric mixtures, diastereomers, and enantiomers, which had to be separated by crystallization, chiral preparative HPLC, or both.[10] To establish an SAR profile and to synthesize larger quantities for in vivo evaluation, we needed to find an enantioselective convergent synthesis of the three-membered benzofuran core, including the formation of two consecutive stereogenic centers, one of which is an all-carbon quaternary center.[11] Moreover, from extensive SAR studies in the AC-131 series, we established that compounds containing halogens in the cycloalkyl and non-phenolic aryl rings, as well as the size of the cycloalkyl ring, gave the most interesting ligands; therefore, reaction conditions to introduce and preserving these functionalities had to be taken into account.

An asymmetric route to synthesize the tricyclic dihydrobenzofuran motif was designed that could be used for both scaffolds. The key intermediates, allylic alcohols **4a**–**c** (Scheme 1), were synthesized. The first step involved the amine-catalyzed iodo-Baylis–Hillman reaction of α,β-unsaturated ketones, producing iodo-carbonyls **2a**–**b** in 82–89% yield.[12] Iodo-carbonyls **2a**–**b** were easily functionalized through a Pd/C-catalyzed Suzuki reaction to efficiently produce aryl ketones **3a**–**d** in 75–91% yield.[13] The aryl ketones **3a**–**c** were subjected to asymmetric oxaborolidine-catalyzed reduction to give cyclic allylic alcohols **4a**–**c** in high yields and high enantiomeric excess. For example, (*S*)-CBS catalyzed the reduction of ketones **3a** and **3c** to yield the (*R*)-alcohols **4a** and **4c** in 98% *ee* and 84% *ee*, respectively. The other enantiomers were obtained using the (*R*)-CBS catalyst.[14]



Scheme 1. Asymmetric synthesis of allylic alcohols **4a**–**d**. *Reagents and conditions*: a) **2a**: I_2, DMAP, 82%, RT, 16 h; b) **2b**: I_2, pyridine, 89%, 0 °C→RT, 16 h; c) Pd/C, Na_2CO_3, $ArB(OH)_2$, 80 °C, 15 min, **3a**: 83%, **3b**: 91%, **3c**: 75%, **3d**: 83%; d) (*S*)-CBS, borane dimethyl sulfide complex, 0 °C→RT, 4 h, **4a**: 83%, 98% *ee*, **4b**: 86%, 96% *ee*, **4c**: 89%, 84% *ee*; e) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, **4d**: 80%, 0 °C, 20 min.

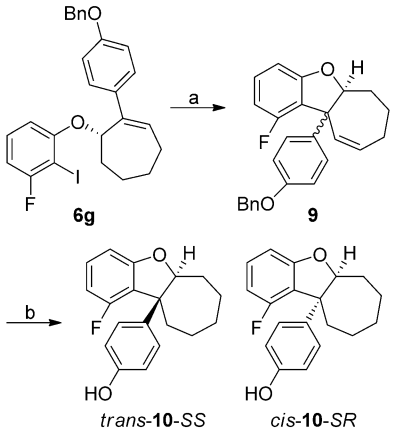
Having established a highly enantioselective and robust method, the cyclic allylic alcohols were further reacted using a Mitsunobu reaction with a set of different iodophenols **5a**–**f** to yield ethers **6a**–**g** (Scheme 2).[15] Next, a palladium-catalyzed intramolecular Mizoroki–Heck coupling using $Pd(OAc)_2$, PPh_3, and Ag_2CO_3 converted ethers **6a**–**g** to the *cis*-fused tricyclic



Scheme 2. Synthesis of benzofurans **8a–g**. *Reagents and conditions*: a) DIAD, PPh_3, toluene, 0 °C→RT, **6a**: 60%, **6b**: 56%, **6c**: 87%, **6d**: 71%, **6e**: 85%, **6f**: 72%, **6g**: 63%; b) $Pd(OAc)_2$, PPh_3, Ag_2CO_3, 80 °C, 16 h, **7a**: 95%, **7b**: 72%, **7c**: 85%, **7d**: 92%, **7e**: 79%, **7f**: quant; c) Pd/C, H_2; RT, overnight, d) H-Cube, Rh/C, 20 °C; e) TBAF, RT, overnight, **8a**: 67%, **8b**: 55%, **8c**: 61%, **8d**: 69%, **8e**: 48%, **8f**: 39%, **8g**: 15%.

benzofurans **7a–f** in high isolated yields as the sole diastereomeric products. However, in a few cases, trace amounts of a double bond isomer were present in a crude NMR sample. Interestingly, when conducting the Heck reaction with the larger cycloheptenyl **9**, a 1:1 mixture of diastereomers was isolated in 72% yield (Scheme 3). The 1:1 *trans*/*cis* ratio of **9** is believed to be the result of the higher flexibility of the cycloheptenyl relative to the cyclohexenyl. In the subsequent step, the benzofuran double bond and the benzyl protecting group were removed by Pd/C under a hydrogen atmosphere to yield the desired dihydrobenzofurans **8a**, **8b**, **8g**,[16] and **10**. The *trans*-**10**-*SS*/*cis*-**10**-*SR* mixture was separated by recrystallization from methanol. By analogy, the *trans*-**10**-*RR*/*cis*-**10**-*RS* isomers were also synthesized. Notably, the use of H_2 and Pd/C was not suitable for the reduction of aryl chloride-containing olefins because the reduction of **7c–e** yielded partial or complete dehalogenation. However, using Rh/C provided a selective and high-yielding reduction of the double bond in 92–95% yields, with only trace amounts of dehalogenation. Finally, the *tert*-butyldimethylsilyl (TBS) protecting group was quantitatively removed by TBAF to give **8c–f**. The *cis*-fused ring system was determined by NOESY NMR experiments, and X-ray crystallography (Figure 3) verified the absolute configuration of compound **8c**.[17]

The synthesis of compounds **16** and **18** started with sequential protection of benzophenone **11** to yield the orthogonally protected **11** (Scheme 4). Treatment of **12** with MeMgBr, followed by acid-mediated elimination, gave **13**. Hydroboration of **13** rendered the terminal alcohol, which was oxidized with DMP to give aldehyde **14** in 47% yield over three steps. Benzofuran **15** was synthesized from **14** (32% yield) by a one-pot quadruple cascade Michael-Robinson-deprotection-oxo-Michael-addition sequence and was isolated as the *cis*-fused dia-



Scheme 3. Synthesis of benzofurans *trans*-**10**-*SS* and *cis*-**10**-*SR*. *Reagents and conditions*: a) $Pd(OAc)_2$, PPh_3, Ag_2CO_3, 72%; b) Pd/C, H_2, 79% (diastereomers separated by recrystallization).

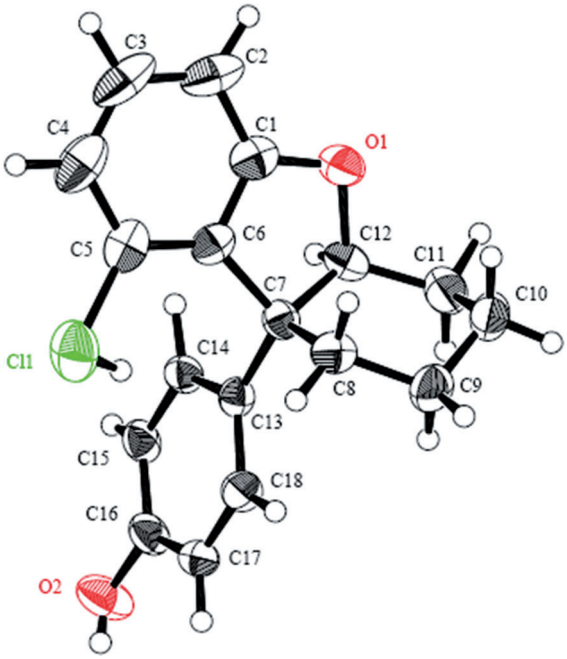
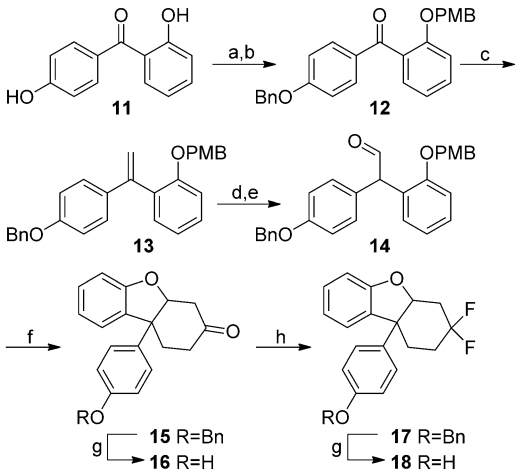


Figure 3. ORTEP rendering of compound **8c**.



Scheme 4. Synthesis of benzofurans **16** and **18**. *Reagents and conditions*: a) BnBr, K_2CO_3; b) (4-methoxyphenyl)methanol, DEAD, PPh_3; c) MeMgBr, HCl (2 M); d) BH_3, NaOH (6 M), H_2O_2; e) DMP, 47%; f) methyl vinyl ketone, KOH (3 M), 32%; g) Pd/C (10%)/H_2, **16**: 60%, **18**: 26%; h) diethylaminosulfur trifluoride 52%.

stereomer. Treatment of compound **15** with diethylaminosulfur trifluoride (DAST) gave a mixture of *gem*-difluoro species **17** and traces of vinyl fluoride in 52% crude yield. Finally, after Pd/C-catalyzed hydrogenolysis of the benzyl, **16**, and **18** could be isolated in 60 and 26% yields, respectively.

All compounds were evaluated in vitro using the proprietary mammalian cell-based functional assay R-SAT (receptor selection and amplification technology), a reporter gene assay, or both (see Supporting Information for details).[18] In general, the compounds were highly active at ERβ and showed high selectivity over ERα, acting as partial or full agonists with efficacies ranging from 80–134%. Unsubstituted compound **8a** has a pEC_{50} value of 7.7 and efficacy of 121% at ERβ and a pEC_{50} of 5.7 and 70% efficacy at ERα (Table 1, entry 3). Introducing a halogen on the aryl moiety (substituent Y) generally improved activity; for example, compounds **8b**–**e** with a halogen substituent at the 3- or 4-position exhibited increased activity relative to **8a** (Table 1, entries 3–6). It should be noted that the potency gradually decreased as the halogen substituent was moved from the 3-position to the 4-position and finally to the 5-position. For example, **8c** with a chloro in the 3-position was 40 times more potent than **8f** with the chloro in the 5-position. In addition, compound **8c** showed nearly 160-fold selectivity for ERβ over ERα. Fluoro-substituted **8b** was less active than **8c**, indicating that the size, electronegativity, or both properties of the aryl substituents are important for potency. Introducing a carbonyl (**16**), by analogy, to SERM-β 1 did not provide the intended interaction and was equipotent with **8a**. Transforming the polar ketone to *gem*-difluoro compound **18** increased the activity over **16** and **8a**. This may be related to an increase in the steric bulk of the cyclohexyl moiety. Moreover, a clear SAR was established for the two scaffolds, i.e., benzofuranol **8g** and benzofuran-phenol **8b**, with only the latter scaffold showing activity. To exclude the possibility that this lack of activity occurred by chance, eight analogues of **8g** were synthesized. However, none of these showed any activity at ERβ (data not shown). The highest activity was observed for cycloheptyl derivative *cis*-**10**-*SR*, with a pEC_{50} value of 9.5 and 80-fold selectivity for ERβ over ERα. The larger cycloheptyl moiety resulted in more active compounds. This trend was also observed in difluorobenzofuran **18**, indicating that a larger and flexible ring can adopt conformations important for selectivity and activity.

Interestingly, when examining the different cycloheptyl isomers, enantiomer *cis*-**10**-*SR* was 40-fold more active than its enantiomer *cis*-**10**-*RS*. Both *trans*-fused diastereomers (*trans*-**10**-*SS* and *trans*-**10**-*RR*) were less active than the most potent *cis* isomer, but were still quite potent, with pEC_{50} values of 8.1

Table 1. In vitro results for ERβ agonists in R-SAT and reporter gene assays.[a]

Entry	Ligand	R-SAT				Reporter Gene Assay				Selectivity[b]
		ERα		ERβ		ERα		ERβ		
		pEC_{50}	Eff. [%]	pEC_{50}	Eff. [%]	pEC_{50}	Eff. [%]	pEC_{50}	Eff. [%]	
1	E2	9.8	100	10.2	100	9.6	100	10.0	100	–
2	AC-131	4.7	63	7.2	90	ND	ND	7.5	119	316/–
3	**8a**	5.5	61	7.6	78	5.7	70	7.7	121	126/100
4	**8b**	–	–	–	–	6.3	61	8.3	134	–/100
5	**8c**	–	–	–	–	6.7	62	8.9	118	–/158
6	**8d**	–	–	–	–	6.7	66	8.5	127	–/63
7	**8e**	–	–	–	–	6.0	62	7.9	109	–/79
8	**8f**	–	–	–	–	<5	37	7.3	89	–/631
9	**8g**	–	–	–	–	5.2	109	–	21	–
10	**16**	<5	43	6.7	87	5.0	52	7.6	110	>50/398
11	**18**	5.3	70	8.0	89	5.5	73	8.4	98	501/794
12	*trans*-**10**-*SS*	<5	30	7.6	80	5.1	60	8.1	98	>398/1000
13	*trans*-**10**-*RR*	<5	45	7.4	59	<5	42	7.3	128	>251/>200
14	*cis*-**10**-*SR*	7.1	107	9.3	91	7.6	68	9.5	90	158/80
15	*cis*-**10**-*RS*	5.0	83	7.6	101	5.6	62	7.9	118	398/158

[a] See the Supporting Information for a detailed description of the R-SAT and reporter gene assays.[18] Agonist efficacies were compared with that of E2; values represent the mean of two or more independent experiments, with each experiment performed at eight doses in triplicate. Standard deviation values for all measurements can be found in the Supporting Information. [b] Selectivity for ERβ over ERα in R-SAT and the reporter gene assay.

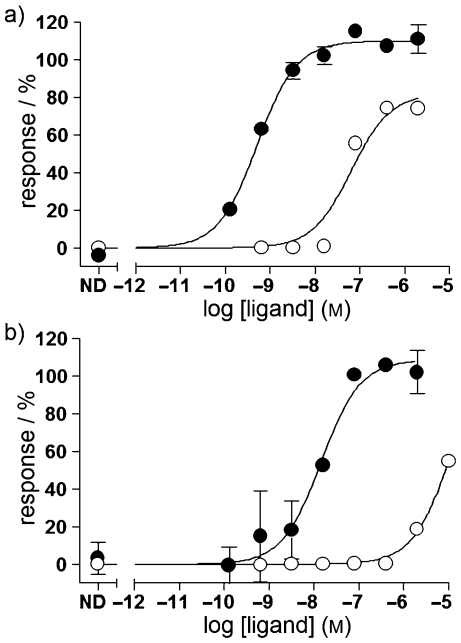


Figure 4. Receptor activity for a) *cis*-**10**-*SR* and b) *trans*-**10**-*SS*. Data are normalized to the response of 17β-estradiol; ●: ERβ, ○: ERα.

and 7.3, respectively (Table 1, entries 11 and 12). More interestingly, *trans*-**10**-*SS* was highly selective at ERβ (1000×) and only a partial agonist at ERα at concentrations up to 10 μM (Figure 4).

ERα and ERβ have two conservative amino acid differences in the ligand binding domain (LBD; Figure 5). In the β-face of the LBD residue, Leu 384 in ERα is replaced with Met 336, while Met 421 in ERα is replaced with Ile 373 in ERβ. These small differences in the LBD make it difficult to achieve selectivity between the two receptors.[19] Several co-crystal structures have been reported for both ERα and ERβ. For ERβ, co-crystals have been reported both with planar ligands that mimic E2 and non-planar ligands such as SERM-β 1.[8b] The non-planar ligands have shown a higher degree of selectivity between the two nuclear estrogen receptors. The non-planar shape of compounds **10** made it reasonable to use the SERM-β 1 co-crystal structure (2GIU.pdb) in our docking studies.[19,20] The phenol in all four isomers of **10** interacts with Glu 305, Arg 346, and water, making the hydrogen bonding network important for obtaining agonist activity. After initial docking, the predicted binding poses were post-processed and minimized with the LBD of ERβ, allowing the amino acid side chains to move around the ligand within a 4 Å distance. The relative calculated MM-GBSA ΔG_{bind} was evaluated and compared with the biological activities. Although it is difficult to use a whole cell functional assay in quantitative evaluations because of the many factors that can influence potency, the calculations correlated well with the in vitro results.[21]

In the predicted models (Figure 5 a–d), the cycloheptyl moiety for all of the isomers is positioned in the same area as the cyclohexenyl group of SERM-β 1, while the benzofuran part projects into the α-face cavity, as observed for the butyl chain of SERM-β 1. Strikingly, depending on the isomer, the cycloheptyl occupies more of the β-face of the LBD to different degrees than does the cyclohexyl of SERM-β 1. The most potent compound, *cis*-**10**-*SR* (pEC_{50} 9.5), had the most favorable binding energy in the docking studies (Figure 5 a). The other three isomers ($pEC_{50} \sim 8$) had 2–4 kcal mol^{-1} higher calculated binding energies. Co-crystals with the non-planar ligands (i.e., SERM-β 1) showed a high degree of flexibility of side chains in the LBD. In the α-face, Phe 377 is shifted, thereby opening a binding pocket and allowing the butyl chain of the

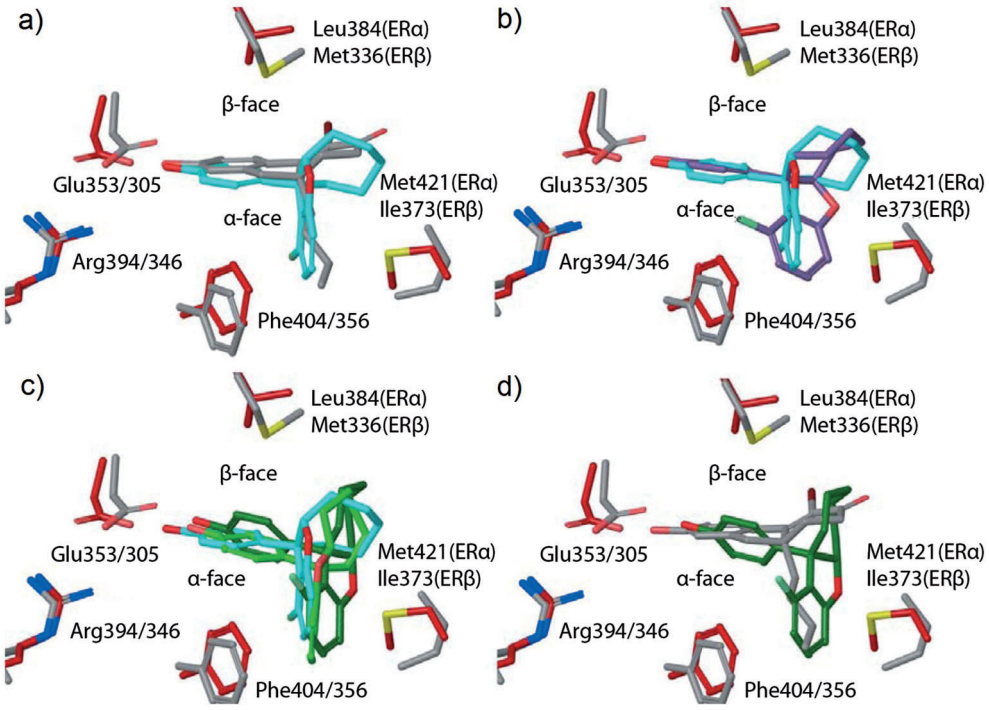


Figure 5. The co-crystal structures of SERM-β 1 (gray) and ERβ (2GIU.pdb, gray residues) overlaid with ERα (1ERE.pdb, red residues). Only important amino acids are shown. a) Proposed binding mode of the most active enantiomer, compound *cis*-**10**-*SR* (light blue), based on docking to 2GIU.pdb. b) Proposed binding mode of both *cis*-fused enantiomers of **10**, *cis*-**10**-*SR* (light blue) and the less active *cis*-**10**-*RS* (purple). c) *cis*-**10**-*SR* (light blue), as well as the less active *trans*-fused diastereomers *trans*-**10**-*SS* (dark green) and *trans*-**10**-*RR* (light green). The rigidity and more pronounced T-shape of the *trans* isomers cause the compounds to protrude into the α-face of the LBD as well as into the β-face. d) SERM-β 1 (gray) and the most selective compound, *trans*-**10**-*SS* (dark green). Withdrawal of *trans*-**10**-*SS* from the Glu 305/Arg 346 residue results in lower potency but also closer proximity to Met 336; this may explain the increased selectivity.

SERM-β 1 to take its place in proximity to Ile 373. These interactions in the α-face appear to explain the selectivity for ERβ. Another strategy was used in the design of the ERβ selective ligand 8β-VE2.[19] In contrast to SERM-β 1, the selectivity of 8β-VE2 is proposed to result from extension into the β-face, where the vinyl group experiences steric repulsion with the Leu 384 in ERα. This does not occur to the same degree with Met 336 in ERβ (thoroughly discussed elsewhere).[19] The less potent *cis* isomer, *cis*-**10**-*RS*, which has an aromatic benzofuran moiety perpendicular toward the edge of Phe 356, does not interact favorably with the accessible pocket (Figure 5 b). The highly ERβ-selective benzofuran *trans*-**10**-*SS* has a benzofuran group in the α-face of the pocket close to Ile 373, similar to SERM-β 1. The cycloheptyl group occupies the β-face of the pocket close to the second amino acid Met 336, causing the phenol to slightly withdraw from Glu 305/Arg 346 (Figure 5 c,d). This causes a gain in selectivity but a loss in potency relative to *cis*-**10**-*SR*. The selectivity can potentially be attributed to steric repulsion in the ERα with Leu 384, similar to 8β-VE2, and a favorable interaction in the α-face, similar to SERM-β 1. Hence, *trans*-**10**-*SS* combines the selectivity features of SERM-β 1 and 8β-VE2.

Conclusions

Selectivity between the two nuclear estrogen receptors is of major concern in using estrogens for chronic treatments, as activation of ERα might lead to severe side effects. We therefore designed a class of highly selective and potent ERβ agonists based on benzofurans as a new molecular scaffold. The compounds presented display a preference for ERβ over ERα and are more active than the parent compound, AC-131. We developed an asymmetric synthesis approach that facilitated investigation of the enantiomers and found *cis*-**10**-*SR* to be the most active compound. More interestingly, the most selective molecule, *trans*-**10**-*SS*, showed a 1000-fold preference for ERβ over ERα and retained very good potency. Based on the predicted binding mode using computational chemistry, we speculate that this is the first ligand to take advantage of the two conservative amino acid differences between ERα and ERβ to achieve selectivity. Molecular modeling showed that the T-shaped topology of *trans*-**10**-*SS* protrudes into the α- and β-faces to gain selectivity at ERβ but at the expense of loss in activity relative to *cis*-**10**-*SR*. Moreover, our SAR study showed that substitution in the 3-position of the aromatic benzofuran is important for biological activity and that *cis*-fused seven-membered rings are more active than smaller six-membered rings. Overall, we have shown that the rigid benzofuran motif is an excellent scaffold to gain high ERβ selectivity and constitutes a good starting point for further development of safe estrogenic treatments.

Experimental Section

General: Chemicals and solvents were purchased from Sigma–Aldrich. Reactions involving oxygen- or moisture-sensitive reagents were carried out under nitrogen atmosphere using anhydrous toluene or THF. Toluene and THF were freshly distilled from benzophenone/sodium. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a JEOL JNM-EX 400 spectrometer at 400 and 100 MHz, respectively, while ^{13}C NMR spectra were recorded on a 500 Varian Unity Inova spectrometer at 126 MHz. Chemical shifts are reported in ppm, with the solvent residual peak as an internal standard ($CHCl_3$ $\delta =$ 7.26 ppm, CDCl3 $\delta = 77.0$ ppm). ^{19}F NMR was measured with ethyl trifluoroacetate as an internal standard (−75.8 ppm) and recorded at 376 MHz on a Varian 400 MHz spectrometer equipped with a Varian OneNMRProbe with a proton observation frequency of 399.95 MHz. The reactions were monitored by thin layer chromatography (TLC) on silica-plated aluminum sheets (silica gel 60 F254, Merck) detecting spots by UV (254 and 365 nm) and cerium molybdate. Flash chromatography was performed on Merck silica gel 60 (0.040–0.063 mm). Optical rotation was measured on a PerkinElmer polarimeter 341 LC. Gas chromatography/mass spectrometry analyses were performed on a Varian Saturn 2000 GC–MS with a Supelco SLB-5ms fused silica capillary column using helium as carrier gas; injector temperature: 300 °C; temperature program: 70 to 330 °C (12 °C min^{-1}); hold time: 4 min. The MS detector consisted of an ion trap with 70 eV ionization. Chiral HPLC chromatography analyses were performed on a Varian 9012Q/9050 UV/Vis detector using HPLC-grade solvents (*n*-hexane and 2-propanol). Purity (>98%) was measured at 254 nm on a Waters 2690/996 photodiode array detector using HPLC-grade solvents (H_2O/0.1% TFA:CH_3CN/0.1% TFA) with an Atlantis T3 5 μm, 4.6×250 mm column. Prep HPLC was done on a Waters 600/2487 dual λ absorbance detector using HPLC-grade solvents; H_2O/0.1% TFA:CH_3CN/0.1% TFA with an Atlantis prep T3 5 μm, 19×250 mm column. HRMS was measured on a Thermo LTQ-OrbitrapXL nano-ES in positive ion mode.

(4-((*tert*-Butyldimethylsilyl)oxy)phenyl)boronic acid: Siloxyphenyl bromide (11.0 g, 38 mmol) was dissolved in THF (70 mL, freshly distilled). The solution was purged with argon and cooled to −75 °C in a CO_2/acetone bath. *N*-Butyllithium (2.5 M in hexanes, 28 mL) was added slowly while maintaining the temperature below −65 °C. A white precipitate formed during the addition. The mixture was stirred for 1 h below −65 °C, then trimethyl borate (26.5 mL, 115 mmol) was added while maintaining the temperature at −65 °C. The resulting clear solution was warmed to room temperature and stirred for 16 h. Concentrated HCl was added until the mixture reached pH 6–7. The reaction mixture was poured into Et_2O (500 mL), and the aqueous layer was discarded. The organic layer was washed three times with H_2O, dried over anhydrous $MgSO_4$, and filtered. The solvent was removed, and the product was recrystallized from EtOAc/pentane to yield the product as an off-white solid in 68% yield (6.6 g): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 8.13 (d, $J = 7.8$ Hz, 2H), 6.97 (d, $J = 7.3$ Hz, 2H), 1.03 (s, 9H), 0.27 ppm (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 159.7$, 137.4, 119.8, 99.9, 25.7, 18.3, −4.3 ppm.

2-(4-((*tert*-Butyldimethylsilyl)oxy)phenyl)cyclohex-2-enone (3 b): General procedure A: DME (6 mL) and H_2O (6 mL) were added to a 20 mL microwave vial containing **2 a**, (668 mg, 3.0 mmol), Na_2CO_3 (637 mg, 6.0 mmol), Ar-$B(OH)_2$ (1517 mg, 6 mmol), and Pd/C (160 mg, 5 mol%). The mixture was degassed by alternating vacuum and N_2 three times, pre-stirred for 5 min, and then subjected to microwave irradiation at 80 °C for 15 min. Without removing the microwave cap, the reaction mixture was extracted with Et_2O (5×5 mL), and the organic phase was dried over (Na_2SO_4), evaporated, and purified by flash chromatography (5:1, pentane/EtOAc) to afford the aryl ketone in 91% yield (824 mg): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.20$ (d, $J = 8.7$ Hz, 2H), 6.98 (t, $J = 4.3$ Hz, 1H), 6.80 (d, $J = 8.7$ Hz, 2H), 2.60–2.55 (m, 2H), 2.53–2.48 (m, 2H), 2.14–2.02 (m,

2H), 0.99 (s, 9H), 0.20 ppm (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 198.3, 155.2, 147.0, 139.7, 129.6, 129.5, 119.5, 39.1, 26.6, 25.6, 22.9, 18.1, −4.5 ppm; MS (EI): *m/z* (%): 302 $[M]^+$ (100), 247 (14), 246 (35), 245 (31), 217 (23).

2-(4-(Benzyloxy)phenyl)cyclohept-2-enone (3c): Following general procedure A, the title compound was obtained after silica gel chromatography as an off-white solid in 75% yield (121 mg): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49–7.30 (m, 5H), 7.21 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 6.70 (t, *J* = 6.5 Hz, 1H), 5.06 (s, 2H), 2.72 (dd, *J* = 7.3, 5.8 Hz, 2H), 2.51 (dd, *J* = 12.0, 6.3 Hz, 2H), 1.97–1.72 ppm (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 205.9, 158.3, 144.1, 140.4, 137.0, 131.6, 129.2, 128.6, 127.9, 127.4, 114.5, 70.0, 43.1, 28.0, 24.9, 22.2 ppm.

2-(2-Fluorophenyl)cyclohex-2-en-1-one (3d): Following general procedure A, purification by flash chromatography (5:1, pentane/EtOAc) afforded the title compound as a white solid in 83% yield (355 mg): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.23 (m, 1H), 7.16 (td, *J* = 7.4, 2.0 Hz, 1H), 7.13–6.98 (m, 3H), 2.57 (t, *J* = 6.7 Hz, 2H), 2.50 (td, *J* = 6.0, 4.3 Hz, 2H), 2.15–2.02 ppm (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 196.3, 159.6 (d, *J* = 247.0 Hz), 149.7 (s), 135.7 (d, *J* = 1.0 Hz), 130.8 (d, *J* = 3.9 Hz), 129.1 (d, *J* = 8.2 Hz), 124.3 (d, *J* = 15.8 Hz), 123.4 (d, *J* = 3.6 Hz), 115.1 (d, *J* = 22.3 Hz), 38.1, 26.0, 22.5 ppm.

(*R*)-2-(4-((*tert*-Butyldimethylsilyl)oxy)phenyl)cyclohex-2-enol (4b): General procedure B: A pre-stirred (10 min, RT) solution of (*S*)-(−)-2-methyl-CBS-oxazaborolidine (357 mg, 1.29 mmol) and borane dimethyl sulfide complex (BMS) (2.36 mL, 4.72 mmol, 2 M solution) in toluene, 30 mL was placed in an ice bath. To the cold reaction mixture was then added a solution of 2-(4-((tert-butyldimethylsilyl)oxy)phenyl)cyclohex-2-enone (1300 mg, 4.30 mmol in toluene, 40 mL) via a syringe pump over 2 h. The reaction was continued for a further 2 h at 0 °C before being quenched with HCl (1 M, 2 mL), diluted with Et_2O (10 mL), extracted, washed with H_2O (10 mL) and brine (10 mL), and dried over $MgSO_4$. The crude product was purified by silica gel chromatography (gradient: pentane → pentane/EtOAc, 1:6) to give the title compound in 86% yield (1100 mg) and 96% *ee*: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 (d, *J* = 8.6 Hz, 2H), 6.81 (d, *J* = 8.6 Hz, 2H), 6.09 (dd, *J* = 4.7, 3.3 Hz, 1H), 4.67 (t, *J* = 3.8 Hz, 1H)), 2.29–2.07 (m, 2H), 2.00–1.91 (m, 1H), 1.88–1.71 (m, 3H), 1.71–1.60 (m, 1H), 1.00 (s, 9H), 0.21 ppm (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.9, 138.3, 133.1, 127.1, 126.9, 120.0, 65.3, 31.5, 26.0, 25.6, 18.2, 17.2, −4.5 ppm; $[\alpha]_D^{20} = +61.0$ (*c* = 1, $CHCl_3$); HPLC: Diacel Chiralpak AD column, *n*-hexane/2-propanol (99:1), flow rate: 1 mL min^{-1}, λ = 254 nm, t_R = 11.2 min (minor) and 12.7 min (major). The racemate was prepared by reducing ketone following general procedure C (see synthesis of **4d** below): MS (EI): *m/z* (%): 304 $[M]^+$ (100), 289 (14), 288 (12), 287 (40), 249 (13), 248 (19), 247 (43), 231 (14), 230 (31), 229 (22), 181 (12), 155 (16), 153 (15).

(*R*)-2-(4-(Benzyloxy)phenyl)cyclohept-2-enol (4c): Following general procedure B, the title compound was obtained after silica gel chromatography in 89% yield (447 mg) and 84% *ee*: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48–7.24 (m, 7H), 7.03–6.87 (m, 2H), 5.97 (dt, *J* = 8.1, 1.8 Hz, 1H), 5.06 (s, 2H), 4.77 (dd, *J* = 7.7, 2.0 Hz, 1H), 2.48–2.35 (m, 1H), 2.29–2.18 (m, 1H), 2.12–1.94 (m, 2H), 1.93–1.51 ppm (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.7, 145.6, 137.0, 135.4, 130.8, 128.5, 127.9, 127.9, 127.4, 114.5, 72.7, 69.9, 33.7, 27.5, 26.7, 25.0, 15.9 ppm; HPLC: Diacel Chiralpak AD column, *n*-hexane/2-propanol (95:5), flow rate: 1 mL min^{-1}, λ = 254 nm, t_R = 17.3 min (minor) and 19.7 min (major).

(*S*)-2-(4-(Benzyloxy)phenyl)cyclohept-2-enol: Following general procedure B, the title compound was obtained after silica gel chromatography in 99% yield (400 mg) and 87% *ee*.

2-(2-Fluorophenyl)cyclohex-2-en-1-ol (4d): General procedure C: **3d** (190 mg, 1 mmol) and $CeCl_3 \cdot 7H_2O$ (360 mg, 1 mmol) were dissolved in 1 mL MeOH. $NaBH_4$ (76 mg, 2 mmol) was added dropwise as a MeOH solution (2 mL) while stirring at 0 °C. The reaction was monitored by TLC and quenched with 2 M HCl, and the mixture was extracted with ether, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography (pentane/EtOAc, 5:1) afforded the title compound as a white solid in 80% yield (154 mg): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (td, *J* = 7.7, 1.8 Hz, 1H), 7.21 (dddd, *J* = 8.1, 7.1, 5.1, 1.8 Hz, 1H), 7.09 (td, *J* = 7.5, 1.3 Hz, 1H), 7.02 (ddd, *J* = 11.0, 8.2, 1.2 Hz, 1H), 5.98 (t, *J* = 3.9 Hz, 1H), 4.59 (t, *J* = 3.8 Hz, 1H), 2.27–2.13 (m, 2H), 1.97–1.87 (m, 1H), 1.86–1.75 (m, 2H), 1.72–1.60 ppm (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.8 (d, *J* = 245.8 Hz), 136.1 (d, *J* = 1.9 Hz), 131.4 (d, *J* = 2.6 Hz), 130.3 (d, *J* = 4.4 Hz), 128.6 (d, *J* = 14.3 Hz), 128.3 (d, *J* = 8.3 Hz), 123.9 (d, *J* = 3.5 Hz), 115.4 (d, *J* = 23.0 Hz), 66.4 (d, *J* = 3.4 Hz), 31.5, 25.7, 17.8 ppm.

(*S*)-1-(4-(Benzyloxy)phenyl)-7-(3-chloro-2-iodophenoxy)cyclohex-1-ene (6c): General procedure D: DIAD (1.03 mL, 6.99 mmol) was added to a stirred solution of **4b** (1120 mg, 3.68 mmol), 3-chloro-2-iodophenol (1872 mg, 7.35 mmol), and PPh_3 (1929 mg, 7.35 mmol) in toluene (50 mL) at 0 °C. The solution was stirred overnight, then diluted with toluene (50 mL) and quenched with NaOH (4 mL, 1 M). The organic layer was separated, washed with H_2O (5 mL) and brine (5 mL), dried over $MgSO_4$, and concentrated. The crude product was purified by flash chromatography (20:1, pentane/EtOAc) to render the product as white crystals in 87% yield (100 mg) and 88% *ee*: mp: 120.8–122.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.17 (d, *J* = 8.6 Hz, 2H), 7.10 (t, *J* = 8.1 Hz, 1H), 6.97 (dd, *J* = 8.0, 1.1 Hz, 1H), 6.68 (dt, *J* = 5.1, 3.0 Hz, 3H), 6.21 (dd, *J* = 5.0, 2.8 Hz, 1H), 5.09 (s, 1H), 2.41–2.26 (m, 1H), 2.18–2.02 (m, 2H), 1.99–1.83 (m, 1H), 1.71–1.51 (m, 2H), 0.91 (s, 9H), 0.11 ppm (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.4, 154.7, 139.9, 134.9, 134.1, 129.8, 129.5, 126.8, 121.6, 119.8, 110.7, 93.4, 73.8, 27.4, 25.8, 25.6, 18.1, 17.1, −4.5 ppm; $[\alpha]_D^{20} = -6.4$ (*c* = 1, $CHCl_3$); HPLC: Diacel Chiralpak AD column, *n*-hexane/2-propanol (9:1), flow rate: 1 mL min^{-1}, λ = 254 nm, t_R = 10.2 min (major) and 12.2 min (minor).

(*S*)-1-(4-(Benzyloxy)phenyl)-7-(5-chloro-2-iodophenoxy)cyclohex-1-ene (6e): Following general procedure D, the title compound was obtained after silica gel chromatography as a colorless oil in 85% yield (602 mg) and 83% *ee*: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (d, *J* = 8.4 Hz, 1H), 7.21 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 2.2 Hz, 1H), 6.74 (d, *J* = 8.7 Hz, 2H), 6.69 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.28 (dd, *J* = 5.0, 2.9 Hz, 1H), 5.13 (t, *J* = 3.0 Hz, 1H), 2.43–2.30 (m, 1H), 2.26–2.11 (m, 2H), 2.03–1.88 (m, 1H), 1.80–1.68 (m, 2H), 0.96 (s, 9H), 0.17 ppm (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.4, 154.8, 140.0, 134.9, 134.9, 134.1, 130.0, 126.9, 122.5, 119.9, 114.1, 85.6, 73.9, 27.5, 25.8, 25.7, 18.2, 17.1, −4.4 ppm; $[\alpha]_D^{20} = -50.4$ (*c* = 6.15, $CHCl_3$); HPLC: Diacel Chiralpak AD column, *n*-hexane/2-propanol (9:1), flow rate: 1 mL min^{-1}, λ = 254 nm, t_R = 8.0 min (major) and 11.0 min (minor).

(*S*)-1-(4-(Benzyloxy)phenyl)-7-(4-chloro-2-iodophenoxy)cyclohex-1-ene (6d): Following general procedure D, the title compound was obtained after silica gel chromatography as a colorless oil in 71% yield (235 mg) and 75% *ee*: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (d, *J* = 2.6 Hz, 1H), 7.24–7.18 (m, 3H), 6.80 (d, *J* = 8.8 Hz, 1H), 6.74 (d, *J* = 8.6 Hz, 2H), 6.27 (dd, *J* = 5.0, 2.9 Hz, 1H), 5.11 (t, *J* = 3.2 Hz, 1H), 2.46–2.34 (m, 1H), 2.26–2.07 (m, 2H), 2.04–1.90 (m, 1H), 1.78–

1.61 (m, 2H), 0.97 (s, 9H), 0.17 ppm (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.7, 154.7, 138.7, 135.0, 134.1, 129.9, 129.0, 126.9, 126.2, 119.9, 114.1, 88.5, 74.0, 27.5, 25.8, 25.7, 18.2, 17.1, −4.4 ppm; $[\alpha]_D^{20} = -32.4$ (c = 1, $CHCl_3$); HPLC: Diacel Chiralpak AD column, *n*-hexane/2-propanol (9:1), flow rate: 1 mL min^{-1}, λ = 254 nm, t_R = 9.3 min (major) and 13.5 min (minor).

(*S*)-1-(4-(Benzyloxy)phenyl)-7-(3-fluoro-2-iodophenoxy)cyclohex-1-ene (6b): Following general procedure D, the title compound was obtained after silica gel chromatography as a colorless oil in 56% yield (100 mg): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.30 (m, 5H), 7.28 (d, J = 8.4 Hz, 2H), 7.24–7.16 (m, 1H), 6.86 (d, J = 8.5 Hz, 2H), 6.70–6.59 (m, 2H), 6.27 (dd, J = 5.0, 2.8 Hz, 1H), 5.16 (t, J = 2.5 Hz, 1H), 5.01 (s, 2H), 2.45–2.33 (m, 1H), 2.26–2.09 (m, 2H), 2.02–1.87 (m, 1H), 1.77–1.59 ppm (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 163.0 (d, J = 244.2 Hz), 158.5 (d, J = 5.7 Hz), 157.9, 137.0, 134.9, 133.9, 130.0, 129.9 (d, J = 9.9 Hz), 128.5, 127.9, 127.4, 127.0, 114.6, 108.8 (d, J = 2.8 Hz), 108.2, 107.9, 73.8, 69.9, 27.5, 25.9, 17.1 ppm.

(*S*)-1-(4-(Benzyloxy)phenyl)-7-(3-fluoro-2-iodophenoxy)cyclohept-1-ene (6g): Following general procedure D, the title compound was isolated after silica gel chromatography as an off-white solid in 63% yield (0.454 mg) and 73% *ee*. Optical purity was increased to 95% *ee* after recrystallization in toluene/MeOH: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48–7.30 (m, 5H), 7.18 (d, J = 8.9 Hz, 2H), 7.04 (td, J = 8.3, 6.7 Hz, 1H), 6.90 (d, J = 8.9 Hz, 2H), 6.60 (ddd, J = 8.4, 7.5, 1.1 Hz, 1H), 6.30 (d, J = 8.4 Hz, 1H), 6.15 (dd, J = 8.0, 6.1 Hz, 1H), 5.27 (d, J = 6.9 Hz, 1H), 5.06 (s, 2H), 2.85–2.73 (m, 1H), 2.49–2.18 (m, 3H), 2.02–1.79 (m, 3H), 1.69–1.55 ppm (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.8 (d, J = 243.7 Hz), 161.5, 158.1 (d, J = 5.8 Hz), 157.7, 142.2, 137.0, 135.8, 134.2, 129.8 (d, J = 9.8 Hz), 129.8 (d, J = 9.8 Hz), 128.6, 127.9, 127.5, 127.0, 114.6, 108.8 (d, J = 2.7 Hz), 107.7 (d, J = 24.3 Hz), 79.2, 75.1 (d, J = 26.3 Hz), 70.0, 31.2, 27.3, 26.7, 26.0 ppm; HPLC: Diacel Chiralpak AD column, *n*-hexane/2-propanol (97:3), flow rate: 1 mL min^{-1}, λ = 254 nm, t_R = 5.7 min (major) and 6.2 min (minor).

(*R*)-1-(4-(benzyloxy)phenyl)-7-(3-fluoro-2-iodophenoxy)cyclohept-1-ene: Following general procedure D, the title compound was isolated after silica gel chromatography as an off-white solid, 69% yield (513 mg) and 71% *ee*.

1-{6-[5-(Benzyloxy)-2-iodophenoxy]cyclohex-1-en-1-yl}-2-fluorobenzene (6f): Following general procedure D, the title compound was obtained after silica gel chromatography (heptane/toluene, 5:1) as a colorless oil in 72% yield (285 mg): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 (d, J = 8.6 Hz, 1H), 7.45–7.35 (m, 5H), 7.25–7.18 (m, 1H), 7.10 (td, J = 7.5, 1.2 Hz, 1H), 7.02 (ddd, J = 10.9, 8.2, 1.1 Hz, 1H), 6.54 (d, J = 2.6 Hz, 1H), 6.36 (dd, J = 8.6, 2.7 Hz, 1H), 6.19 (d, J = 3.9 Hz, 1H), 5.22 (t, J = 3.6 Hz, 1H), 4.98 (s, 2H), 2.45–2.35 (m, 1H), 2.31–2.21 (m, 1H), 2.16–1.98 (m, 2H), 1.97–1.86 (m, 1H), 1.78–1.67 ppm (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.1, 159.9 (d, J = 243.2 Hz) 158.6, 157.6, 139.0, 136.5, 133.7 (d, J = 2.0 Hz), 132.8 (d, J = 1.2 Hz), 130.9 (d, J = 4.2 Hz), 129.0 (d, J = 14.2 Hz), 128.5, 128.4 (d, J = 8.3 Hz), 128.0, 127.4, 124.0 (d, J = 3.4 Hz), 115.2 (d, J = 22.8 Hz), 108.4, 102.2, 77.3, 74.2 (d, J = 3.3 Hz), 70.1, 27.7, 25.7, 17.5 ppm.

***tert*-Butyl(4-[(1*R*,9*S*)-3-chloro-8-oxatricyclo[7.4.0.0^{2,7}]trideca-2(7),3,5,12-tetraen-1-yl]phenoxy) dimethylsilane (7c)**: General procedure E: a solution of aryl ether **6c** (148 mg, 0.27 mmol) in toluene (20 mL) was added to a 20 mL microwave vial containing Ag_2CO_3 (226 mg, 0.82 mol), PPh_3 (21 mg, 0.082 mmol), and $Pd(OAc)_2$ (9.2 mg, 0.04 mmol). The vial was sealed, and the reaction mixture was evacuated and flushed with nitrogen three times and heated at 80 °C for 16 h. The reaction mixture was filtered through a plug of Celite, concentrated, and purified by silica gel chromatography (pentane/EtOAc, 20:1) to yield the cyclic product as a colorless oil in 85% yield (96 mg): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20–7.07 (m, 4.7H, overlapping), 6.84–6.71 (m, 5.9H overlapping), 6.12–6.06 (m, 0.5H, minor), 6.06–6.03 (m, 2H), 5.93–5.86 (m, 0.1H, minor), 4.80 (dd, J = 4.8, 4.0 Hz, 0.3H, minor), 4.75 (t, J = 2.9 Hz, 1H), 3.03–2.74 (m, 0.2H, minor), 2.58–2.38 (m, 0.2H, minor), 2.38–2.25 (m, 1H), 2.23–2.00 (m, 2H), 1.85–1.72 (m, 1H), 0.98 (s, 9H), 0.97 (s, 3.3H, minor), 0.20 (s, 6H), 0.19 ppm (s, 2.0H, minor); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.4, 161.2, 154.6, 154.2, 137.7, 136.3, 133.0, 131.2, 131.0, 130.8, 129.7, 129.6, 128.8, 128.5, 128.2, 128.0, 126.7, 125.1, 122.2, 122.1, 119.9, 119.9, 108.7, 108.3, 91.3, 90.1, 54.0, 31.3, 28.0, 25.8, 25.8, 21.6, 19.1, 18.6, 18.3, 18.3, −4.3 ppm; $[\alpha]_D^{20} = +14.0$ (c = 1, $CHCl_3$); MS (EI): *m/z* (%): 415 [M+H]$^+$ (13), 414 [M]$^+$ (44), 413 [M+H]$^+$ (100), 360, (10), 359 (25), 358 (10), 357 (11), 207 (12), 205 (14), 205 (35).

***tert*-Butyl(4-[(1*R*,9*S*)-5-chloro-8-oxatricyclo[7.4.0.0^{2,7}]trideca-2(7),3,5,12-tetraen-1-yl]phenoxy) dimethylsilane (7e)**: Following the general procedure E, the title compound was isolated after silica gel chromatography as a colorless oil in 79% yield (120 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18 (d, J = 8.5 Hz, 2H), 6.86–6.83 (m, 3H), 6.79 (d, J = 8.4 Hz, 2H), 5.96 (ddd, J = 10.0, 5.5, 2.1 Hz, 7H), 5.63 (d, J = 10.1 Hz, 1H), 4.74 (t, J = 1.6 Hz, 1H), 2.38–2.25 (m, 7H), 2.19–1.99 (m, 2H), 1.83–1.72 (m, 7H), 0.98 (s, 9H), 0.20 ppm (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.8, 154.7, 136.3, 133.6, 133.4, 129.3, 129.2, 127.0, 125.3, 121.0, 119.8, 110.7, 90.5, 52.9, 25.6, 21.5, 18.9, 18.2, −4.4 ppm; $[\alpha]_D^{20} = +11.8$ (c = 1, $CHCl_3$); MS (EI): *m/z* (%): 415 [M+H]$^+$ (15), 414 [M]$^+$ (45), 413 [M+H]$^+$ (34), 412 (100), 384 (11), 271 (10), 209 (26), 205 (29), 177 (10).

***tert*-Butyl(4-[(1*R*,9*S*)-4-chloro-8-oxatricyclo[7.4.0.0^{2,7}]trideca-2(7),3,5,12-tetraen-1-yl]phenoxy) dimethylsilane (7d)**: Following general procedure E, the title compound was isolated after silica gel chromatography as a colorless oil in 92% yield (112 mg): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 (d, J = 8.4 Hz, 2H), 7.12 (ddd, J = 8.5, 2.3, 0.6 Hz, 1H), 6.94 (d, J = 2.3 Hz, 1H), 6.82 (d, J = 8.4 Hz, 2H), 6.77 (d, J = 8.5 Hz, 1H), 6.00 (ddd, J = 9.8, 5.4, 1.9 Hz, 1H), 5.66 (d, J = 10.1 Hz, 1H), 4.75 (t, J = 9.8, 1.82 Hz, 1H), 2.40–2.27 (m, 1H), 2.21–2.02 (m, 2H), 1.86–1.68 (m, 1H), 1.00 (s, 9H), 0.23 ppm (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.6, 154.7, 136.5, 136.1, 129.2, 129.1, 128.2, 127.2, 125.4, 124.8, 119.8, 110.9, 90.3, 53.5, 25.6, 21.4, 18.9, 18.2, −4.4 ppm; $[\alpha]_D^{20} = +31.3$ (c = 1, $CHCl_3$); MS (EI): *m/z* (%): 415 [M+H]$^+$ (12), 414 [M]$^+$ (38), 413 [M+H]$^+$ (32), 412 (89), 177 (19).

(2*R*,7*S*)-2-[4-(benzyloxy)phenyl]-13-fluoro-8-oxatricyclo[7.4.0.0^{2,7}]trideca-1(9),3,10,12-tetraene (7b): Following general procedure E, the title compound was obtained and used without further purification in the next step.

1-[4-(Benzyloxy)phenyl]-3-fluoro-8-oxatricyclo[7.5.0.0^{2,7}]tetradeca-2,4,6,13-tetraene (9): Following general procedure E, the title compound was isolated after silica gel chromatography as a colorless oil in a 72% yield (119 mg), and 1:1 diastereomeric ratio: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48–7.27(m, 4H, major, 4H minor), 7.23–7.07 (m, 1H major, 1H minor), 6.96 (d, J = 8.9 Hz, 2H major), 6.89 (d, J = 8.9 Hz, 2H minor), 6.80–6.50 (m, 2H major, 2H minor), 6.17–5.86 (m, 2H major, 2H minor), 5.06 (s, 2H (major)), 5.03 (s, 2H (minor)), 5.00 (dd, J = 12.2, 5.2 Hz, 1H (minor)), 4.81 (dd, J = 8.8, 2.2 Hz, 1H (major)), 2.34–2.06 (m, 4H major, 4H minor), 2.04–1.80 (m, 2H major, 2H minor), 1.75–1.65 (m, 1H major, 1H minor), 1.62–1.43 ppm (m, 1H major, 1H minor); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.8 (d, J = 9.3 Hz), 160.4 (d, J =

8.9 Hz), 159.1 (d, J=248.8 Hz), 158.9 (d, J=248.7 Hz), 157.7, 157.6, 137.2, 137.0, 133.5, 133.0, 131.3 (d, J=3.6 Hz), 130.51, 130.48, 129.9 (d, J=9.0 Hz), 129.5 (d, J=8.8 Hz), 128.9, 128.8, 128.5, 128.5, 127.91, 127.90, 127.7, 127.5, 127.5, 124.3 (d, J=18.1 Hz), 120.9 (d, J=17.3 Hz), 114.7, 114.2, 108.8 (d, J=20.7 Hz), 108.2 (d, J=20.8 Hz), 106.6 (d, J=3.4 Hz), 105.9 (d, J=3.4 Hz), 94.1, 91.3, 70.0, 69.9, 59.1 (d, J=3.0 Hz), 56.7 (d, J=2.7 Hz), 28.8, 28.1, 27.4, 26.6, 20.6, 19.8 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ=−75.80 (s), −118.25 (dd, J=9.4, 5.8 Hz), −120.95 ppm (dd, J=9.3, 5.7 Hz).

11-(Benzyloxy)-2-(2-fluorophenyl)-8-oxatricyclo[7.4.0.0^{2,7}]trideca-1(9),3,10,12-tetraene (7 f): Following general procedure E, the title compound could not be sufficiently purified by silica gel chromatography and was therefore used without further purification in the next step.

***tert*-Butyl(4-[(1*R*,9*S*)-3-chloro-8-oxatricyclo[7.4.0.0^{2,7}]trideca-2(7),3,5-trien-1-yl]phenoxy) dimethylsilane**: General procedure F: **7 c** in EtOH was subjected to hydrogen cube-mediated reduction conditions using Rh/C (0.5 mL min^{-1}, 20 °C, full H_2-mode). The reaction mixture was looped until full conversion was observed by GC–MS (approximately seven loops). The saturated title compound was isolated in 92% yield (92 mg): ^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.22 (d, J=8.6 Hz, 2H), 7.06 (t, J=8.0 Hz, 1H), 6.84–6.68 (m, 4H), 4.77 (t, J=3.0 Hz, 1H), 2.63–2.51 (m, 1H), 2.11–1.98 (m, 1H), 1.97–1.83 (m, 1H), 1.76–1.45 (m, 5H), 0.98 (s, 9H), 0.19 ppm (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=160.5, 154.2, 136.5, 134.9, 130.6, 129.2, 128.7, 122.2, 119.8, 108.6, 91.0, 52.0, 30.2, 25.8, 25.4, 20.9, 18.8, 18.3, −4.3 ppm; $[\alpha]_D^{20}$=−9.5 (c=1, $CHCl_3$); MS (EI): m/z (%): 416 $[M]^+$ (43), 415 $[M]^+$ (34), 414 $[M]^+$ (100), 360 (12), 359 (21), 358 (31), 357 (31), 209 (24), 208 (15), 207 (53), 179 (15), 125 (10).

***tert*-Butyl(4-[(1*R*,9*S*)-5-chloro-8-oxatricyclo[7.4.0.0^{2,7}]trideca-2(7),3,5-trien-1-yl]phenoxy)dimethylsilane**: Following general procedure F, the title compound was isolated after silica gel chromatography as a colorless oil in 95% yield (10 mg): ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.18 (d, J=8.7 Hz, 2H), 6.81 (ddd, J=26.0, 11.0, 4.7 Hz, 5H), 4.86 (t, J=4.1 Hz, 1H), 2.28 (dd, J=14.5, 6.9 Hz, 1H), 2.03–1.91 (m, 1H), 1.82–1.69 (m, 3H), 1.68–1.47 ppm (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=159.7, 154.2, 136.9, 136.7, 133.1, 128.4, 124.3, 120.8, 119.7, 110.8, 90.7, 50.6, 33.7, 26.1, 25.7, 21.3, 19.4, 18.2, −4.4 ppm; $[\alpha]_D^{20}$=−18.7 (c=1, $CHCl_3$); MS (EI): m/z (%): 416 $[M]^+$ (41), 415 $[M]^+$ (33), 414 $[M]^+$ (100), 360 (12), 359 (7), 358 (20), 209 (11), 207 (20), 179 (11).

***tert*-Butyl(4-[(1*R*,9*S*)-4-chloro-8-oxatricyclo[7.4.0.0^{2,7}]trideca-2(7),3,5-trien-1-yl]phenoxy) dimethylsilane**: Following general procedure F, the title compound was isolated after silica gel chromatography as a colorless oil in 95% yield (10 mg): ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.20 (d, J=8.7 Hz, 2H), 7.08 (dd, J=8.4, 2.3 Hz, 1H), 6.82–6.74 (m, 4H), 4.85 (t, J=3.9 Hz, 1H), 2.29 (dd, J=9.3, 5.1 Hz, 1H), 2.00 (dd, J=14.0, 3.9 Hz, 1H), 1.81–1.49 ppm (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=157.5, 154.3, 140.4, 136.1, 128.5, 127.7, 125.4, 123.8, 119.8, 111.0, 90.3, 51.2, 33.8, 26.0, 25.7, 21.4, 19.5, 18.2, −4.4 ppm; $[\alpha]_D^{20}$=+27.5 (c=1, $CHCl_3$); MS (EI): m/z (%): 416 $[M]^+$ (43), 415 $[M]^+$ (35), 414 $[M]^+$ (100), 360 (8), 359 (12), 358 (17), 209 (9), 207 (27), 179 (12).

4-[(1*R*,9*S*)-3-Chloro-8-oxatricyclo[7.4.0.0^{2,7}]trideca-2(7),3,5-trien-1-yl]phenol (8 c): General procedure G: TBAF (1 M) was added to a vial containing *tert*-butyl(4-[(1*R*,9*S*)-3-chloro-8-oxatricyclo[7.4.0.0^{2,7}]trideca-2(7),3,5-trien-1-yl]phenoxy)dimethylsilane in THF (5 mL). The reaction was stirred overnight and quenched with 1 mL H_2O. Et_2O (20 mL) was added, and the organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by silica gel chromatography (gradient: 10:1–5:1, pentane/EtOAc) and then C18 preparative chromatography ((H_2O, 0.1% TFA)/(CH_3CN/H_2O, 95:5, 0.1% TFA), gradient: 0→100%), at 15 mL min^{-1} to give the title compound as a white solid in 71% yield (46 mg): ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.25 (d, J=6.8 Hz, 1H), 7.07 (dd, J=8.2, 7.8 Hz, 1H), 6.81–6.78 (m, 1H), 6.77 (d, J=8.0 Hz, 1H), 4.75 (t, J=3.1 Hz, 1H), 4.65 (s, 1H), 2.63–2.49 (m, 1H), 2.11–1.88 (m, 1H), 1.67–1.57 ppm (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=160.2, 154.0, 136.0, 134.5, 130.5, 129.2, 128.8, 122.2, 115.1, 108.6, 90.9, 51.9, 30.0, 25.3, 20.8, 18.6 ppm; $[\alpha]_D^{20}$=−12.6 (c=1, $CHCl_3$); MS (EI): m/z (%): 302 $[M]^+$ (37), 301 $[M]^+$ (23), 300 $[M]^+$ (100), 259 (18), 258 (21), 257 (45), 154 (11), 160 (10), 159 (12); HRMS-ESI: m/z $[M+H]^+$ calcd for $C_{18}H_{18}ClO_2$: 301.0995, found: 301.0988.

4-[(1*R*,9*S*)-3-Chloro-8-oxatricyclo[7.4.0.0^{2,7}]trideca-2(7),3,5,12-tetraen-1-yl]phenol (8 d): Following general procedure G, the title compound was isolated after C18 preparative chromatography ((H_2O, 0.1%TFA)/(CH_3CN/H_2O, 95:5, 0.1% TFA) gradient: 0→100%) at 15 mL min^{-1} as a clear oil in 69% yield (5 mg): ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.18 (d, J=8.6 Hz, 1H), 7.10 (t, J=8.0 Hz, 1H), 6.85–6.78 (m, 3H), 6.75 (d, J=8.0 Hz, 1H), 6.10–5.99 (m, 2H), 4.72 (t, J=2.9 Hz, 1H), 2.41–2.24 (m, 1H), 2.19–2.01 (m, 2H), 1.84–1.71 ppm (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=161.3, 154.3, 135.9, 130.91, 130.85, 129.6, 129.0, 128.3, 126.5, 122.1, 115.2, 108.7, 90.0, 53.9, 21.4, 18.9 ppm; HRMS-ESI: m/z $[M+H]^+$ calcd for $C_{18}H_{16}ClO_2$: 299.0839, found: 299.0822.

4-[(1*R*,9*S*)-5-Chloro-8-oxatricyclo[7.4.0.0^{2,7}]trideca-2(7),3,5-trien-1-yl]phenol (8 f): Following general procedure G, the title compound was isolated after C18 preparative chromatography ((H_2O, 0.1%TFA)/(CH_3CN/H_2O, 95:5, 0.1% TFA) gradient: 0→100%) at 15 mL min^{-1} as a clear oil in 41% yield (3 mg): ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.20 (d, J=8.8 Hz, 2H), 6.89–6.67 (m, 5H), 4.84 (t, J=4.1 Hz, 1H), 2.32–2.19 (m, 1H), 2.04–1.92 (m, 1H), 1.82–1.46 ppm (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=159.6, 154.0, 136.8, 136.4, 133.2, 128.7, 124.2, 120.8, 115.1, 110.9, 90.7, 50.6, 33.6, 26.1, 21.3, 19.4 ppm; $[\alpha]_D^{20}$=−27.6 (c=0.38, $CHCl_3$); MS (EI): m/z (%): 302 $[M]^+$ (35), 301 $[M]^+$ (24), 300 $[M]^+$ (100), 259 (35), 258 (18), 257 (92), 222 (15), 194 (10); HRMS-ESI: m/z $[M+H]^+$ calcd for $C_{18}H_{18}ClO_2$: 301.0995, found: 301.0988.

4-[(1*R*,9*S*)-4-Chloro-8-oxatricyclo[7.4.0.0^{2,7}]trideca-2(7),3,5-trien-1-yl]phenol (8 e): Following general procedure G, the title compound was isolated after C18 preparative chromatography ((H_2O, 0.1%TFA)/(CH_3CN/H_2O 95:5, 0.1% TFA)) gradient: 0→100%), 15 mL min^{-1} as a clear oil in 51% yield (3.7 mg): ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.23 (d, J=8.9 Hz, 2H), 7.08 (dd, J=8.4, 2.3 Hz, 1H), 6.83–6.75 (m, 4H), 4.85 (t, J=3.9 Hz, 1H), 2.36–2.23 (m, 1H), 2.07–1.96 (m, 1H), 1.84–1.47 ppm (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=157.4, 154.1, 147.4, 140.3, 128.8, 127.8, 123.8, 115.2, 111.1, 99.9, 90.4, 51.1, 33.7, 26.0, 21.4, 19.5 ppm; $[\alpha]_D^{20}$=+24.5 (c=0.4, $CHCl_3$); MS (EI): m/z (%): 302 $[M]^+$ (35), 301 $[M]^+$ (22), 300 $[M]^+$ (100), 259 (19), 258 (11), 257 (52), 194 (16), 145 (10); HRMS-ESI: m/z $[M+H]^+$ calcd for $C_{18}H_{18}ClO_2$: 301.0995, found: 301.0979.

4-[(1*R*,9*S*)-3-Fluoro-8-oxatricyclo[7.4.0.0^{2,7}]trideca-2(7),3,5-trien-1-yl]phenol (8 b): General procedure H: **7 b** (36 mg, 0.097 mmol) was dissolved in EtOH (5 mL), followed by addition of Pd/C (10 mg, 10% wt). The reaction was purged three times by alternating vacuum and H_2, after which the reaction mixture stirred overnight (16 h) under an atmosphere of H_2. The mixture was filtered through a pad of Celite, concentrated, and purified by silica gel chromatography to yield a white solid in 55% yield (15 mg): ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.23 (d, J=8.7 Hz, 2H), 7.12 (td, J=8.1, 5.8 Hz, 1H), 6.78 (d, J=8.8 Hz, 2H), 6.65 (d, J=8.0 Hz, 1H), 6.55

(t, J=8.8 Hz, 1H), 4.88 (s, 1H), 4.83 (t, J=4.5 Hz, 1H), 2.31 (d, J=5.0 Hz, 1H), 2.13 (d, J=7.6 Hz, 1H), 1.99–1.75 (m, 2H), 1.74–1.39 ppm (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=161.1 (d, J=9.2 Hz), 159.5 (d, J=247.9 Hz), 154.1, 137.2, 129.6 (d, J=8.8 Hz), 128.0, 122.3 (d, J=18.0 Hz), 115.2, 108.2 (d, J=20.9), 106.3, 90.5, 51.5, 31.8, 26.2, 20.9, 18.9 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ=−75.8 (s), −120.2 ppm (dd, J=9.2, 5.8 Hz). $[\alpha]_D^{20}=-6.0$ (c=1, $CHCl_3$); MS (EI): m/z (%): 285 $[M]^+$ (35), 284 $[M]^+$ (100), 242 (10), 241 (48), 191 (20); HRMS-ESI: m/z $[M+H]^+$ calcd for $C_{19}H_{20}FO_2$: 285.1291, found: 285.1283.

4-{3-Fluoro-8-oxatricyclo[7.5.0.0^{2,7}]tetradeca-2,4,6-trien-1-yl}phenol (10): Following general procedure H, the title compound was purified by silica gel chromatography to yield a white solid in 79% yield (147 mg). The diastereomers were separated by dissolving the white solid in MeOH (1.5 mL) and separating the mother liquor (dr 2, *cis*-**10**-*SR*) from the remaining white solid (dr 1, *trans*-**10**-*SS*). This procedure was repeated until a diastereomerically pure compound could be observed.

trans*-10-*SS: Mp: 275–277 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.34 (d, J=8.8 Hz, 2H), 7.02 (td, J=8.2, 5.7 Hz, 1H), 6.72 (d, J=8.9 Hz, 2H), 6.64 (d, J=8.0 Hz, 1H), 6.42 (dd, J=9.3, 8.5 Hz, 1H), 4.94 (dd, J=11.5, 6.2 Hz, 1H), 4.59 (s, 1H), 3.34–3.21 (m, 1H), 2.32–2.07 (m, 2H), 2.00–1.77 (m, 3H), 1.72–1.58 (m, 2H), 1.51–1.40 (m, 1H), 1.04–0.81 ppm (m, 1H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ=159.7 (d, J=9.8 Hz), 158.3 (d, J=246.1 Hz), 155.7, 131.1, 129.5 (d, J=8.8 Hz), 127.3, 126.4 (d, J=18.4 Hz), 115.0, 108.1 (d, J=20.9 Hz), 106.6, 91.9, 53.4, 32.6, 26.7, 25.7, 24.2, 22.5 ppm; $[\alpha]_D^{20}=+189.0$ (c=1, EtOAc); MS (EI): m/z (%): 299 $[M]^+$ (22), 298 $[M]^+$ (100), 241 (40), 205 (17); ^{19}F NMR (376 MHz, [D$_6$]DMSO): δ=−75.8 (s), −121.0 ppm (dd, J=9.4, 6.0 Hz); HRMS-ESI: m/z $[M+H]^+$ calcd for $C_{19}H_{20}FO_2$: 299.1447, found: 299.1440.

cis*-10-*SR: Mp: 156.4–159.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.20–7.14 (m, 1H), 7.11 (d, J=8.4 Hz, 2H), 6.75 (d, J=8.8 Hz, 2H), 6.64 (dd, J=8.0, 0.5 Hz, 1H), 6.56 (t, J=9.0 Hz, 1H), 4.90 (dd, J=6.6, 1.6 Hz, 1H), 4.66 (s, 1H), 2.40–2.26 (m, 2H), 2.19 (dt, J=12.9, 5.2 Hz, 1H), 1.90–1.79 (m, 1H), 1.75–1.53 (m, 4H), 1.43–1.28 (m, 1H), 1.18–1.04 ppm (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=161.2 (d, J=9.7 Hz), 159.5 (d, J=248.2 Hz), 153.9 (s), 140.6 (s), 130.1 (d, J=9.1 Hz), 127.1 (s), 119.6 (d, J=18.0 Hz), 115.3 (s), 107.6 (d, J=21.0 Hz), 105.4 (d, J=3.3 Hz), 95.1 (d, J=0.8 Hz), 57.4 (d, J=2.9 Hz), 36.3 (d, J=1.3 Hz), 31.3, 31.1, 25.7, 23.1 ppm; $[\alpha]_D^{20}=+15.2$ (c=1, $CHCl_3$); MS (EI): m/z (%): 299 $[M]^+$ (21), 298 $[M]^+$ (100), 242 (12), 241 (51); ^{19}F NMR (376 MHz, $CDCl_3$): δ=−75.8 (s), −117.9 ppm (s); HRMS-ESI: m/z $[M+H]^+$ calcd for $C_{19}H_{20}FO_2$: 299.1447, found: 299.1441.

1-(2-Fluorophenyl)-8-oxatricyclo[7.4.0.0^{2,7}]trideca-2(7),3,5-trien-5-ol (8g): Following general procedure H, the title compound was isolated as a colorless oil after silica gel chromatography in 15% yield (5 g) over two steps: ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.24–7.17 (m, 1H), 7.04 (ddd, J=12.4, 8.1, 1.3 Hz, 1H), 6.98 (dd, J=7.8, 1.3 Hz, 1H), 6.96 (d, J=8.0 Hz, 1H), 6.89 (td, J=8.1, 1.8 Hz, 1H), 6.44 (dd, J=8.0, 2.3 Hz, 1H), 6.40 (d, J=2.2 Hz, 1H), 5.13 (ddd, J=7.0, 5.5, 1.9 Hz, 1H), 2.40–2.29 (m, 1H), 2.07–1.98 (m, 2H), 1.74–1.57 (m, 3H), 1.57–1.45 (m, 1H), 1.43–1.30 ppm (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=161.0 (d, J=247.0 Hz), 160.5, 156.5, 133.7 (d, J=10.0 Hz), 128.9 (d, J=4.4 Hz), 128.5 (d, J=8.9 Hz), 124.9, 124.8, 123.8 (d, J=3.4 Hz), 116.5 (d, J=23.2 Hz), 107.3, 98.8 (s), 88.3 (d, J=5.0 Hz), 50.5 (d, J=3.2 Hz), 31.9 (d, J=3.6 Hz), 28.0, 21.2, 19.6 ppm; HRMS-ESI: m/z $[M+H]^+$ calcd for $C_{19}H_{20}FO_2$: 285.1291, found: 285.1281.

2-{[4-(Benzyloxy)phenyl]carbonyl}phenol: 4-[(2-Hydroxyphenyl)-carbonyl]phenol (3 g, 14 mmol), benzyl bromide (1.7 mL, 14.1 mmol), and K_2CO_3 (3.9 g, 28 mmol) were stirred at reflux overnight in CH_3CN (30 mL). The reaction mixture was filtered through Celite and evaporated. The crude mixture was purified by silica gel chromatography to yield the title compound in 54% yield (2.3 g): ^{1}H NMR (400 MHz, $CDCl_3$): δ=11.97 (s, 1H), 7.72 (d, J=8.8 Hz, 2H), 7.64 (dd, J=8.0, 1.7 Hz, 1H), 7.52–7.34 (m, 5H), 7.08 (d, J=8.9 Hz, 3H), 6.92–6.86 (m, 1H), 5.17 ppm (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=200.0, 162.9, 162.0, 136.1, 135.8, 133.2, 131.8, 130.5, 128.7, 128.2, 127.5, 119.3, 118.5, 118.3, 114.5, 70.2 ppm.

[4-(Benzyloxy)phenyl]({2-[(4-methoxyphenyl)methoxy]phenyl})-methanone (12): (4-Methoxyphenyl)methanol (2.1 g, 15.6 mmol), PPh_3 (3.4 g, 13 mmol), 2-{[4-(benzyloxy)phenyl]carbonyl}phenol (4 g, 13 mmol), THF (20 mL), and DEAD (5.9 mL, 13 mmol, 40% in toluene) were added to a flask and stirred at room temperature. The reaction was quenched after 16 h, concentrated, and purified using silica gel chromatography (pentane/EtOAc, 20:1–5:1–3:1) to yield compound **12**: ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.80 (d, J=8.8 Hz, 1H), 7.49–7.32 (m, 2H), 7.09–6.93 (m, 2H), 6.76 (d, J=8.7 Hz, 1H), 5.12 (s, 2H), 4.96 (s, 2H), 3.76 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=195.2, 162.6, 159.1, 156.1, 136.2, 132.1, 131.4, 131.3, 129.9, 129.4, 128.6, 128.6, 128.4, 128.2, 127.4, 120.8, 114.3, 113.7, 113.1, 70.1, 70.0, 55.2 ppm.

1-(1-(4-(Benzyloxy)phenyl)vinyl)-2-((4-methoxybenzyl)oxy)benzene (13): MeMgBr (16.6 mmol, 3 M) was added to a stirred solution of **12** (4.7 g, 11 mmol) in THF at 0 °C; this was allowed to reach RT, was stirred for 72 h, and was quenched with 2 M HCl, extracted with Et_2O (2×50 mL), dried over Na_2SO_4, and reduced in vacuo. The title compound was difficult to purify and was therefore used without further purification in the next reaction.

2-(4-(Benzyloxy)phenyl)-2-(2-((4-methoxybenzyl)oxy)phenyl)ethanol: BF_3 (16.4 mL, 1 M in THF) was added to a stirred solution of **13** (3.5 g, 8.2 mmol) in THF (20 mL) at 0 °C until complete conversion of the alkene was observed by TLC. The mixture was again cooled to 0 °C before subsequent addition of H_2O in THF (10%), NaOH (6 M, 13.7 mL), and H_2O_2 (10.6 mL) and allowed to reach RT. The mixture was stirred overnight, after which the mixture was adjusted to ~pH 2 with HCl (2 M) and extracted with Et_2O, dried over $MgSO_4$, and evaporated. The title compound was difficult to purify and was used without further purification in the next reaction.

2-(4-(Benzyloxy)phenyl)-2-(2-((4-methoxybenzyl)oxy)phenyl)acetaldehyde (14): 2-(4-(Benzyloxy)phenyl)-2-(2-((4-methoxybenzyl)oxy)phenyl)ethanol (2.8 g, 6.2 mmol) dissolved in CH_2Cl_2 (1 mL) was added to a stirred solution of Dess–Martin reagent (3.4 g, 8.1 mmol) in CH_2Cl_2 (40 mL) and left to stir for 16 h. The suspension was then evaporated and directly purified by silica gel chromatography to yield aldehyde **14** in 47% yield (2.3 g) over three steps: ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.79 (d, J=1.3 Hz, 1H), 7.35–7.20 (m, 5H), 7.15–7.11 (m, 3H), 7.01 (d, J=8.7 Hz, 2H), 6.95 (dd, J=7.5, 1.6 Hz, 1H), 6.88 (d, J=8.3 Hz, 1H), 6.85 (d, J=8.7 Hz, 2H), 6.78 (d, J=8.7 Hz, 2H), 5.02 (s, 1H), 4.94 (s, 2H), 4.88 (s, 2H), 3.69 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=199.4, 159.4, 158.0, 156.0, 136.9, 130.6, 130.1, 129.1, 128.7, 128.6, 128.5, 128.2, 127.9, 127.4, 126.6, 121.0, 115.0, 113.9, 112.1, 70.0, 70.0, 58.0, 55.2 ppm.

9b-(4-(Benzyloxy)phenyl)-1,4,4a,9b-tetrahydrodibenzo[*b*,*d*]furan-3(2*H*)-one (15): A solution of KOH in EtOH (7.6 μL, 3 M) was added to a mixture of **14** (100 mg, 023 mmol) and methyl vinyl ketone (0.021 mL, 0.25 mmol) in THF (3 mL) at 0 °C. The reaction was allowed to reach room temperature and was stirred overnight. The mixture was neutralized with HCl (2 M) and diluted with Et_2O

(10 mL), and the organic layer was extracted, dried over Na_2SO_4, and concentrated. The reaction mixture was re-dissolved in EtOH (10 mL), and conc. HCl (1 mL) was added. The mixture was heated to reflux for 3 h, then diluted with Et_2O (10 mL) and washed with $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated. The crude product was purified by silica gel chromatography (gradient: 10:1–5:1–1:1, pentane/EtOAc) to yield the title compound as a clear oil in 32% yield (27 mg): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.33 (m, 6H), 7.30 (d, J = 8.8 Hz, 2H), 7.20 (t, J = 7.6 Hz, 1H), 6.97 (d, J = 8.1 Hz, 2H), 6.92 (t, J = 7.3 Hz, 1H), 6.84 (d, J = 8.1 Hz, 1H), 5.13 (t, J = 3.1 Hz, 1H), 5.07 (s, 2H), 2.85 (ddd, J = 40.0, 17.0, 3.2 Hz, 2H), 2.73 (td, J = 14.0, 3.3 Hz, 1H), 2.41 (dt, J = 18.3, 3.3 Hz, 1H), 2.27 (dt, J = 13.8, 3.7 Hz, 1H), 2.02 ppm (ddd, J = 18.4, 14.2, 4.2 Hz, 1H).

9b-(4-Hydroxyphenyl)-1,4,4a,9b-tetrahydrodibenzo[*b*,*d*]furan-3(2*H*)-one (16): Following general procedure H, the title compound was isolated after silica gel chromatography in 60% yield (5 mg): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.23 (m, 3H), 7.19 (ddd, J = 8.1, 7.1, 1.7 Hz, 1H), 6.98–6.89 (m, 2H), 6.82 (d, J = 8.9 Hz, 2H), 5.12 (t, J = 3.2 Hz, 1H), 4.93 (s, 1H), 2.85 (ddd, J = 40.6, 17.0, 3.3 Hz, 2H), 2.71 (td, J = 14.1, 3.5 Hz, 1H), 2.41 (dt, J = 18.4, 3.4 Hz, 1H), 2.26 (dt, J = 13.9, 3.8 Hz, 1H), 2.01 ppm (ddd, J = 18.4, 14.2, 3.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 209.2, 159.5, 154.5, 138.1, 132.8, 129.1, 128.0, 124.9, 121.5, 115.5, 109.7, 89.3, 51.8, 41.8, 35.9, 31.6 ppm; HRMS-ESI: m/z $[M+H]^+$ calcd for $C_{18}H_{17}O_3$: 281.1178, found: 281.1188.

9b-(4-(Benzyloxy)phenyl)-3,3-difluoro-1,2,3,4,4a,9b-hexahydrodibenzo[*b*,*d*]furan (17): DAST (0.129 g, 0.29 mmol, 50% wild-type in CH_2Cl_2) was added to a stirred solution of **16** (0.027 g, 0.037 mmol) in CH_2Cl_2 (1 mL). The mixture was stirred overnight and filtered to give a mixture of *gem*-difluoro species with traces of vinyl fluoride in a crude yield of 52%. The reaction was used without further purification in the next step.

4-(7,7-Difluoro-5a,6,7,8,9,9a-hexahydrodibenzo[*b*,*d*]furan-9a-yl)-phenol (*gem*-difluoro) (18) and 4-(7-fluoro-5a,6,9,9a-tetrahydrodibenzo[*b*,*d*]furan-9a-yl)phenol (vinyl fluoride): Following general procedure H, the *gem*-difluoro was isolated after silica gel chromatography in 26% yield (3 g): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20–7.14 (m, 1H), 7.07 (d, J = 8.8 Hz, 2H), 6.97 (dd, J = 7.4, 1.5 Hz, 1H), 6.90 (td, J = 7.4, 0.9 Hz, 1H), 6.85 (d, J = 8.0 Hz, 1H), 6.73 (d, J = 8.8 Hz, 2H), 5.02–4.96 (m, 1H), 4.69 (s, 1H), 2.44–2.24 (m, 3H), 2.22–2.12 (m, 1H), 2.11–1.95 (m, 1H), 1.92–1.74 ppm (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.5, 154.4, 136.5, 133.7, 129.0, 128.2, 124.1, 122.65 (d, J = 242.8 Hz), 121.4, 115.4, 110.8, 87.9 (dd, J = 6.6, 4.3 Hz), 51.4 (s), 35.6 (d, J = 25.5 Hz), 30.6 (t, J = 24.2 Hz), 30.2 ppm (dd, J = 6.4, 3.6 Hz).

Abbreviations: estrogen receptor α (ERα), estrogen receptor β (ERβ), 17β-estradiol (E2), diethylaminosulfur trifluoride (DAST), 4-dimethylaminopyridine, (DMAP), diethyl azodicarboxylate (DEAD), diisopropyl azodicarboxylate (DIAD), Dess–Martin periodinane (DMP), structure–activity relationship (SAR), tetrabutylammonium fluoride (TBAF).

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