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Synthesis and Structure–Activity Relationships of 1-Benzylindane Derivatives as Selective Agonists for Estrogen Receptor Beta

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Abstract

The estrogen receptor beta (ERβ) selective agonist is considered a promising candidate for the treatment of estrogen deficiency symptoms in ERβ-expressing tissues,

without the risk of breast cancer, and multiple classes of compounds have been reported as ERβ selective agonists. Among them, 6-6 bicyclic ring-containing structures (e.g., isoflavone phytoestrogens) are regarded as one of the cyclized analogues of isobutestrol **5b**, and suggest that other cyclized scaffolds comprising 5-6 bicyclic rings could also act as selective ERβ ligands.

In this study, we evaluated the selective ERβ agonistic activity of 1-(4-hydroxybenzyl)indan-5-ol **7a** and studied structure–activity relationship (SAR) of its derivatives. Some functional groups improved the properties of **7a**; introduction of a nitrile group on the indane-1-position resulted in higher selectivity for ERβ (**12a**), and further substitution with a fluoro or a methyl group to the pendant phenyl ring was also preferable (**12b**, **d**, and **e**). Subsequent chiral resolution of **12a** identified that ***R*-12a** has a superior profile over ***S*-12a**. This is comparable to diarylpropionitrile (DPN) **5c**, one of the promising selective ERβ agonists and indicates that this indane-based scaffold has the potential to provide better ERβ agonistic probes.

1. Introduction

Estrogens play a crucial role in the development, maintenance, and functioning of the reproductive system and nonreproductive tissues such as cardiovascular,

musculoskeletal, immune, and central nervous systems in both males and females.[1,2] While estrogens can be beneficial for health, the proliferative effect of estrogens may increase the risk of cancer in the breast and uterus.[3,4] Hormone replacement therapy (HRT) reduces many symptoms such as hot flashes, sweating, and bone loss in postmenopausal women; however, long-term use of estrogens increases the risk of breast cancer.[5,6]

The multiple actions of estrogens are exerted through two estrogen receptors, ERα[7,8] and ERβ,[9,10] which have different patterns of tissue distribution and biological regulation.[11] The ERα, expressed at high levels in the uterus and breast is now considered to involve a proliferative effect and can bring about malignant growth in these tissues, whereas ERβ has an antiproliferative effect on breast cancer cells.[12,13] Thus, an ERβ selective ligand is considered to exert beneficial effects on ERβ-expressing tissues, such as the prostate, colon, and brain, without the risk of breast cancer.[14,15]

Although ERα and ERβ share less than 60% sequence homology in the ligand-binding domain (LBD), the ligand-binding pockets (LBPs) of the two isoforms have a difference of only two amino acids; Leu384 and Met421 in ERα are substituted

with Met336 and Ile373 in ERβ, respectively.[16] In fact, 17β-estradiol (**E2**, an endogenous estrogen) binds to both ERs without selectivity.

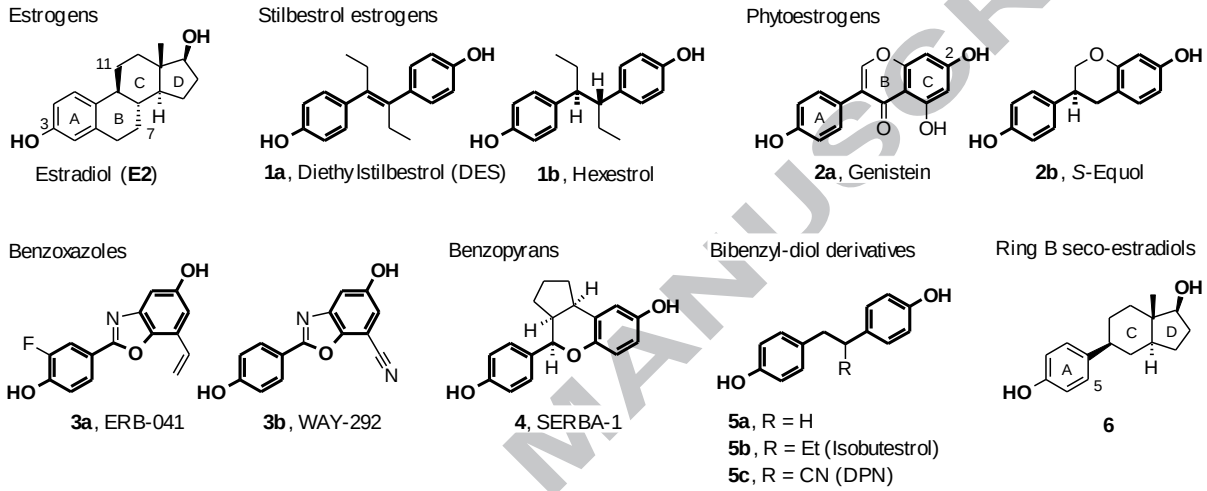


Figure 1. Estradiol and ERβ ligands.

To date, multiple classes of compounds have been reported as ERβ selective agonists.[17,18] Among them, 1,2-bis(4-hydroxyphenyl)ethane **5a** is one of the common templates for ER ligands, and the exact motif or its oxygen-containing analogues are incorporated into many scaffolds (Fig. 1). The representative phytoestrogen genistein **2a**,[19] daidzein enteric metabolite *S*-equol **2b**,[20] and synthetic ligands ERB-041 **3a**,[21] WAY-292 **3b**,[21] and SERBA-1 **4**,[22] are relatively rigid molecules comprising fused-ring frameworks. On the other hand, ERβ ligands with more structural flexibility, such as bibenzyl-diol derivatives **5a**–**c**, are also known. Diarylpropionitrile (DPN) **5c** is an

attractive ligand with a 72-fold binding selectivity relative to **E2**,[23] and isobutestrol **5b** with a nonpolar ethyl group instead of the cyano group in DPN **5c** also exerts an 18-fold relative binding selectivity for ERβ.[24]

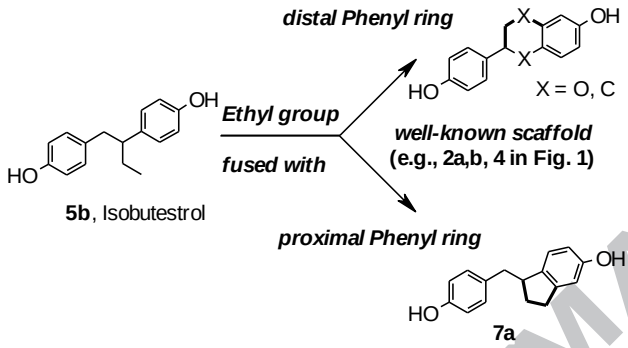


Figure 2. Compounds of interest.

As illustrated in Fig. 2, the cyclized scaffold of **5b** fused between the ethyl group and the distal phenyl ring provides well-known ERβ selective ligands with a 6-6 bicyclic ring (e.g., compounds **2a**, **2b**, and **4**). Fusing the ethyl group of **5b** to the proximal phenyl ring affords a 1-benzylindane framework, and it is also expected to be a promising scaffold as ERβ selective ligand; however, little is known about the estrogenic actions of such compounds. In a previous report, 1-(4-hydroxybenzyl)indan-5-ol **7a** with a 5-6 bicyclic ring may have exhibited antigonadotropic activity and a weak estrogenic effect;[25] however, the actions for ERs

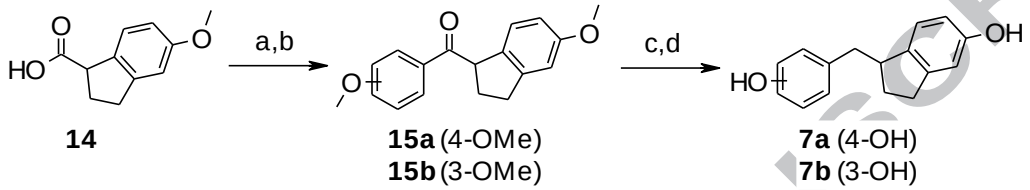
and ERβ selectivity remain unidentified. Therefore, we were intrigued by the possibility of a 1-benzylindane scaffold as novel ERβ selective ligands, and investigated whether **7a** and its derivatives have selective ERβ agonistic activity.

Herein, we report that **7a** is an attractive template for ERβ selective agonists and disclose the SARs of the 1-benzylindane derivatives, some of which have excellent agonistic activities and high selectivities for ERβ in terms of binding affinities and transcriptional activities.

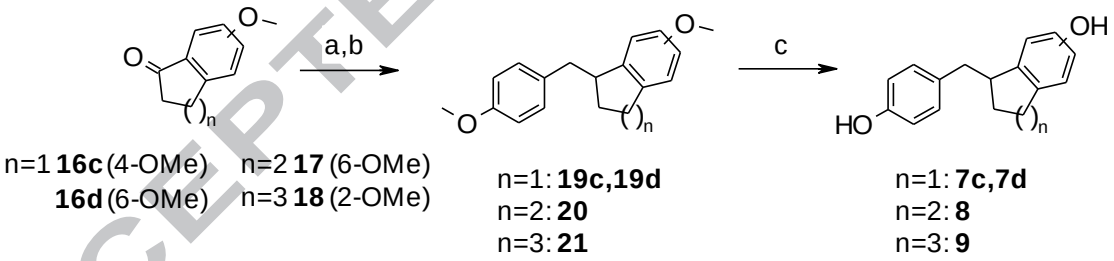
2. Chemistry

The synthesis of racemic compounds evaluated in this article is illustrated in Schemes 1–6. Hydroxy-substituted indane derivatives and ring-expanded analogues bearing benzyl groups were prepared from carboxylic acid **14** or ketones **16c**,**d**, **17**, and **18**. Compounds **7a**,**b** were obtained by reduction of the carbonyl group with Et_3SiH and subsequent demethylation of the methoxy groups by BBr_3 for the benzoyl derivatives **15a**,**b**, prepared by addition of the corresponding phenyl Grignard reagents to the Weinreb amide obtained from **14** (Scheme 1). When using ketones as starting materials, catalytic hydrogenation of the benzylic hydroxy groups generated by addition of benzyl

Grignard reagent, followed by demethylation, afforded compounds **7c**,**d**, **8**, and **9** (Scheme 2).

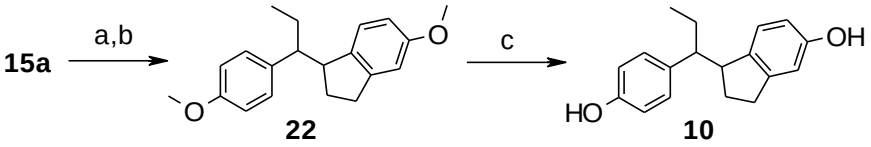


Scheme 1. Reagents and conditions: (a) MeONHMe·HCl, EDCI·HCl, HOBt·H_2O, Et_3N, CH_2Cl_2, 0 °C to rt; (b) 4-(or 3-)MeO–PhMgBr, THF, 0 °C to rt; (c) Et_3SiH, TFA, 0 °C to rt; (d) BBr_3, CH_2Cl_2, −78 °C to rt.



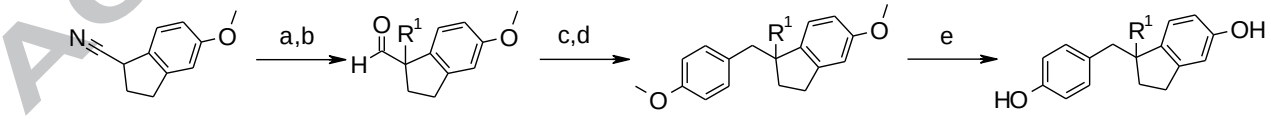
Scheme 2. Reagents and conditions: (a) 4-MeO–BnMgCl, THF, Toluene, 0 °C to rt; (b) Pd–C, H_2, MeOH, THF, rt; (c) BBr_3, CH_2Cl_2, −78 °C to rt.

Using the above intermediate **15a**, the ethyl-substituted derivative **10** was obtained via Wittig olefination and catalytic hydrogenation of the double bond, followed by demethylation (Scheme 3).



Scheme 3. Reagents and conditions: (a) $EtP^{+}Ph_3Br^{-}$, *n*-BuLi, THF, 0 °C to rt; (b) Pd–C, H_2, MeOH, THF, rt; (c) BBr_3, CH_2Cl_2, −78 °C to rt.

The synthesis of 1-alkylated-1-benzylindane derivatives **11a**–**d** was achieved by alkylation of cyanide **23** with alkyl iodides in the presence of NaH and subsequent conversion of the nitrile groups into 4-methoxybenzyl groups before demethylation. The nitrile groups of the alkylated intermediates were reduced into aldehydes **24a**–**d** using DIBAL-H and then reacted with lithiated anisole, followed by removal of the resulting hydroxy group as described above (Scheme 4).



23

24a (R^1=Me)
24b (R^1=Et)
24c (R^1=*n*-Pr)
24d (R^1=*n*-Bu)

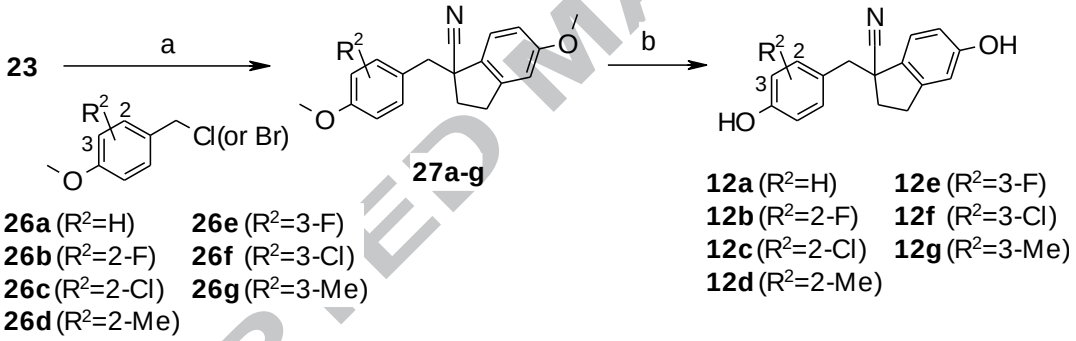
25a (R^1=Me)
25b (R^1=Et)
25c (R^1=*n*-Pr)
25d (R^1=*n*-Bu)

11a (R^1=Me)
11b (R^1=Et)
11c (R^1=*n*-Pr)
11d (R^1=*n*-Bu)

Scheme 4. Reagents and conditions: (a) NaH, R^1-I, DMF, 0 °C to rt; (b) DIBAL-H,

Toluene, −78 °C, then 2 M HCl aq., rt; (c) 4-Br-anisole, *n*-BuLi, THF, −78 °C to rt; (d) Pd–C, H_2, MeOH, THF, rt; (e) BBr_3, CH_2Cl_2, −78 °C to rt.

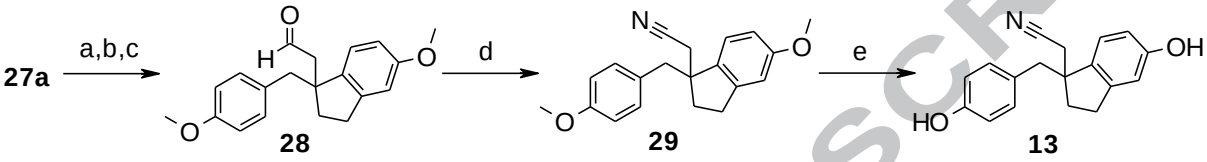
The 1-cyano derivatives **12a**–**g** were more easily prepared by introduction of various benzyl groups onto the nitrile-substituted carbon under modified conditions of the above alkylation and subsequent demethylation (Scheme 5).



Scheme 5. Reagents and conditions: (a) **26a**–**g**, LDA, THF, −78 °C to rt; (b) BBr_3, CH_2Cl_2, −78 °C to rt.

Homologation of the aldehyde obtained by reduction of the above intermediate **27a** was achieved by acidic hydrolysis of the methyl enol ether prepared by the Wittig reaction, and conversion of the formyl group into a nitrile group by heating with

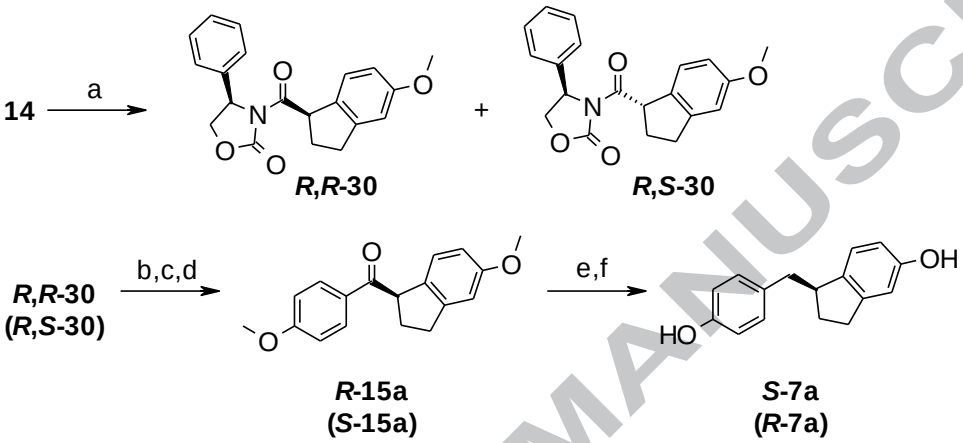
hydroxylamine hydrochloride, followed by demethylation of the 1-cyanomethyl product **29**, afforded compound **13** (Scheme 6).



Scheme 6. Reagents and conditions: (a) DIBAL-H, Toluene, −78 °C, then 2 M HCl aq., rt; (b) $MeOCH_2P^+Ph_3Cl^-$, *n*-BuLi, THF, 0 °C to rt; (c) HCl, THF, 75 °C; (d) $HO–NH_2·HCl$, NMP, 130 °C; (e) Pyridine·HCl, 220 °C.

Preparations of each enantiomer of the key compounds **7a** and **12a** are described in Schemes 7 and 8. In the synthesis of the 1-unsubstituted-1-benzylindane enantiomers ***S*-7a** and ***R*-7a**, the corresponding chiral benzoyl intermediates ***R*-15a** and ***S*-15a** were prepared, respectively. Chiral resolution was achieved by flash column chromatography on silica gel of the diastereomixture of chiral oxazolidinone derivatives ***R*,*R*-30** and ***R*,*S*-30**, obtained by acylation of the oxazolidinone nitrogen with the acid chloride of **14** using *n*-BuLi as a base. In each separated diastereomer, the other isomer was not detected by NMR spectroscopy. After removal of the chiral auxiliary using lithium hydrogen peroxide, ***S*-7a** and ***R*-7a** were synthesized in a manner similar to that of

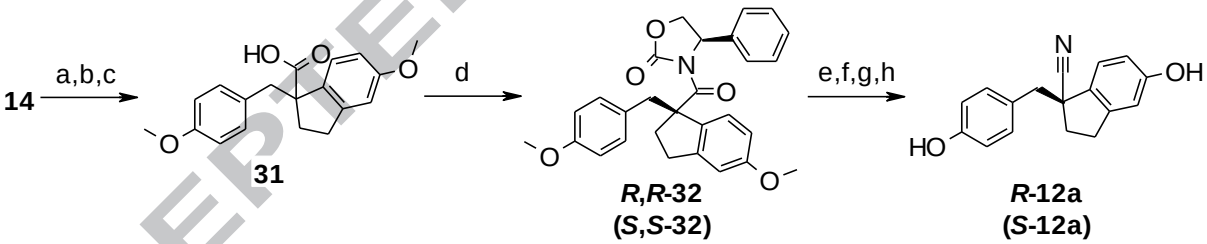
racemate **7a**. The optical purity of each enantiomer was confirmed to be >98% ee by high performance liquid chromatography (HPLC) analysis (Scheme 7).



Scheme 7. Reagents and conditions: (a) (i) $(COCl)_2$, CH_2Cl_2, rt; (ii) (*R*)-4-Ph-oxazolidin-2-one, *n*-BuLi, THF, −78 °C to rt; (b) $LiOH·H_2O$, H_2O_2, THF, H_2O, 0 °C; (c) MeONHMe·HCl, EDCI·HCl, $HOBt·H_2O$, Et_3N, CH_2Cl_2, 0 °C to rt; (d) 4-MeO–PhMgBr, THF, 0 °C; (e) Et_3SiH, TFA, 0 °C to rt; (f) BBr_3, CH_2Cl_2, −78 °C to rt.

Chiral 1-cyano derivatives ***R*-12a** and ***S*-12a** were also synthesized from **14**. For resolution, (*R*)-oxazolidinone chiral auxiliary was similarly introduced into 1-benzylindane-1-carboxylic acid **31** as described above, in which **31** was prepared by 1-benzylation of the methyl ester of **14** and subsequent hydrolysis. Although the two

diastereomers ***R*,*R*-32** and ***R*,*S*-32** were not separable by flash column chromatography, pure ***R*,*R*-32** was fortunately obtained as a single diastereomer by recrystallization from ethyl acetate/*n*-hexane. After removal of the chiral auxiliary, the resulting chiral carboxylic acid was converted into cyanide via carboxamide in a general manner, followed by demethylation to provide ***R*-12a**. In the synthesis of ***S*-12a**, (*S*)-oxazolidinone was used instead of the (*R*)-isomer, as a chiral auxiliary. In each enantiomer obtained by these methods, the other enantiomer was not detected by HPLC analysis (Scheme 8).



Scheme 8. Reagents and conditions: (a) H_2SO_4, MeOH, 70 °C; (b) 4-MeO–BnCl, LDA, THF, −78 °C to rt; (c) LiOH·H_2O, THF, MeOH, H_2O, rt; (d) (i) $(COCl)_2$, CH_2Cl_2, rt; (ii) (*R*) (or (*S*))-4-Ph-oxazolin-2-one, *n*-BuLi, THF, −78 °C to rt; (iii) recrystallization; (e) LiOH·H_2O, H_2O_2, THF, H_2O, 0 °C; (f) CDI, THF, rt, then NH_3 aq., rt; (g) TFAA, Et_3N, CH_2Cl_2, 0 °C to rt; (h) BBr_3, CH_2Cl_2, −78 °C to rt.

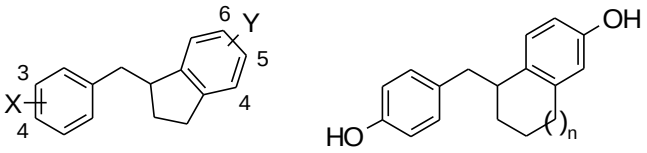
The absolute configurations of ***R*-7a**, ***S*-7a**, ***R*-12a**, and ***S*-12a** were determined based on their corresponding intermediates.[26]

3. Results and Discussion

The relative binding affinities (RBAs) of test compounds for ERs were determined by a fluorescence polarization displacement assay using commercial estrogen receptor competitor assay kits. The correlations of the RBA values and selectivities of the reference compounds **5a**–**c** listed in Table 1 were comparable to the literature values[27] measured in competitive radiometric binding assays. To further study the agonistic properties, the transcriptional activities were evaluated by a cell-based reporter gene assay in HEK293T cells transiently transfected with either ERα or ERβ expression plasmid, the estrogen responsive element (ERE)-driven luciferase plasmid, and the internal control plasmid. These results are presented in Tables 1–3.

To prove the hypothesis that **7a** might be an ERβ agonist, we evaluated the binding affinities with ERs. Expectedly, **7a** showed high RBA for ERβ. The RBA value of 67.8% on ERβ observed in **7a** was higher than DPN **5c**, the selectivity for ERβ (6.8-fold) was also higher than isobutestrol **5b**, and subsequent assessment of the transcriptional activities revealed that **7a** was an ERβ selective agonist (Table 1).

Table 1. Binding affinities and transcriptional activities for ERs and ERβ selectivities of 1-benzylindane derivative **7a** and related compounds.



7a-d **8** (n=1), **9** (n=2)

Ligand	X	Y	RBA[a] (%)			Log *P*[c]	Transcriptional acitivity EC_{50}[d] (nM)		
			hERα	hERβ	β/α[b]		hERα	hERβ	Rel.β/α[e]
E2	-	-	100	100	1	*3.75*	0.35 ± 0.03	0.04 ± 0.01	1
5a	-	-	0.9 ± 0.2	11.7 ± 1.6	13	*3.90*	*47%*[f]	7.12 ± 0.53	-
5b	-	-	27.2 ± 11.6	100 ± 14	3.7	*4.63*	185 ± 17	0.23 ± 0.01	101
5c	-	-	1.6 ± 0.9	37.0 ± 11.1	23	*3.18*	2,390 ± 89	0.82 ± 0.07	372
7a	4-OH	5-OH	9.9 ± 3.6	67.8 ± 9.4	6.8	*4.24*	1,170 ± 265	1.14 ± 0.21	131
7b	3-OH	5-OH	3.1 ± 1.5	11.6 ± 0.6	3.7	*4.24*	3,090 ± 535	32.5 ± 7.2	12
7c	4-OH	4-OH	5.6 ± 2.0	17.3 ± 5.9	3.1	*4.24*	1,830 ± 101	72.4 ± 29.7	3
7d	4-OH	6-OH	4.1 ± 1.2	21.3 ± 4.3	5.2	*4.24*	2,110 ± 498	25.9 ± 7.1	10
8	-	-	35.4 ± 20.7	91.6 ± 38.6	2.6	*4.68*	102 ± 30	0.18 ± 0.03	71
9	-	-	62.6 ± 28.4	98.9 ± 9.8	1.6	*5.13*	123 ± 45	0.15 ± 0.05	103

[a]Relative binding affinity (RBA) values were calculated by IC_{50}[**E2**]/IC_{50}[test compound] × 100 (RBA of **E2** = 100), shown as mean ± SD of three or four independent experiments, performed in duplicate.

[b]β/α values = ERβ-RBA/ERα-RBA (ERβ selectivity of binding affinity).

[c]Log *P* values were calculated using Marvin 6. 2. 0 (ChemAxon).

[d]EC_{50} values are shown as Mean ± SD of three independent experiments, performed in duplicate.

[e]Rel.β/α values = {ERβ-EC_{50}[**E2**]/ERβ-EC_{50}[compound]}/{ERα-EC_{50}[**E2**]/ERα-EC_{50}[compound]} (ERβ selectivity of agonistic activity).

[f]The value is the reporter activation at 10 μM, normalized by the maximum response of **E2**, which is set as 100%.

Because two hydroxy groups at both ends of many ER ligands would play an important role in achieving high binding affinities and transcriptional activities by interacting with the Glu-Arg-water triad (Glu353/Arg394 in ERα, Glu305/Arg346 in ERβ) and His (His524 in ERα, His475 in ERβ),[17] we next evaluated the optimal position of each hydroxy group of **7a**. By moving the hydroxy group on the pendant phenyl ring

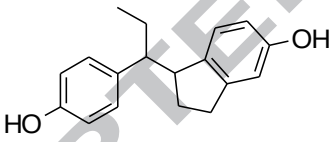
of **7a** from the 4-position to the 3-position (**7a** vs **7b**), a 6-fold decrease in RBA for ERβ was observed. On the indane ring, 4-hydroxy and 6-hydroxy analogues also showed 4-fold (**7c**) and 3-fold (**7d**) diminished RBAs for ERβ, compared to substitution in the 5-position, respectively. Although reduced RBAs for ERα were also observed in compounds **7b**–**d**, the resulting selectivities for ERβ were decreased. Additionally, remarkable losses in agonistic activities and ERβ selectivities were observed in the reporter gene assay. Thus, each hydroxy group in the original position of **7a** was considered to be optimal, indicating that these groups are involved in forming favorable hydrogen bonds with the receptor, like those of other ER agonists. Among the two hydrogen bonds observed in the complex structures of **E2** with ERs,[28,29] the interaction of the estradiol-3-hydroxy group with the Glu-Arg-water triad is considered to be effective for maintaining the affinity of **E2**. More profound effects on the affinities observed in 4-hydroxy group on the pendant phenyl ring suggested that this group faced toward Glu-Arg-water triad in ERs. Further, the estimated distance between two hydroxy groups of **7a** (12.0 Å)[30] was comparable to that of genistein **2a** (12.1 Å),[16] suggesting that the hydroxy group on the indane ring is able to form a hydrogen bond with the His475, supported by the alignment of **2a** in the X-ray crystal structure complexed with ERβ.[16]

To determine the optimum size of the bicyclic ring, we next evaluated ring-expanded analogues with 6- and 7-membered aliphatic rings (**8**, **9**). The improvement of the RBA value on ERβ was observed in both analogues, but loss of selectivity was observed because of the higher effect on ERα. Since the volume of the LBP of ERα is proposed to be larger than that of ERβ,[31] these ring-expanded analogues were assumed to be more efficiently filling the larger cavity of ERα.

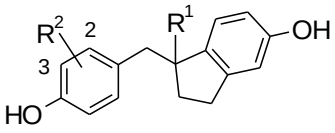
Thus, **7a** was determined to be an optimal template for exploring substituent effects. We next attempted to introduce functional groups onto the linker carbons between the two phenyl rings. The results of the ring-expanded analogues described above suggested that modifications at the 2- and 3-positions of the indane ring might increase ERα affinities; therefore, substitution at these positions was avoided. By introduction of an ethyl group into the methylene carbon of the 1-benzyl group, one of the highest RBA values of 122% on ERβ in this study was observed with compound **10**; however, the selectivity was almost abrogated by about a 10-fold increase in the RBA for ERα (Table 2). A similar SAR is known in the case of stilbene compounds. Diethylstilbestrol (DES) **1a** has two ethyl groups filling in two regions of ERα-LBP not occupied by **E2**, located at the 7α and 11β positions of **E2**,[32] and removal of one of the ethyl groups results in reduction of binding affinities, whereas its ERβ selectivity is

improved.[27] A similar relationship has been reported between hexestrol **1b** and isobutestrol **5b**.[27] Compound **10** is a cyclic analogue of hexestrol **1b** formed by connecting one ethyl group to its proximal phenyl ring. The 5-membered aliphatic ring of indane might partially play a role as one ethyl group of hexestrol **1b**; thus, **10** exhibited the highest RBA for both ERs with a remarkable loss in selectivity.

Table 2. Binding affinities and transcriptional activities for ERs and ERβ selectivities of 1-benzylindane derivatives with substitutions on linker carbons and the pendant phenyl group.



10



11a-d, 12a-g, 13

Ligand	R^1	R^2	RBA[a] (%)			Log *P*[c]	Transcriptional acitivity EC_{50}[d] (nM)		
			hERα	hERβ	β/α[b]		hERα	hERβ	Rel.β/α[e]
10	-	-	88.9 ± 39.7	122 ± 21	1.4	*4.97*	6.33 ± 0.80	0.10 ± 0.01	8
11a	Me	H	17.0 ± 3.2	90.2 ± 38.7	5.3	*4.54*	481 ± 101	0.43 ± 0.17	144
11b	Et	H	32.9 ± 15.9	82.6 ± 11.7	2.5	*4.98*	116 ± 12	0.36 ± 0.05	41
11c	*n*-Pr	H	50.9 ± 22.9	100 ± 19	2.0	*5.43*	169 ± 6	0.53 ± 0.06	40

11d	*n*-Bu	H	13.0 ± 7.7	42.0 ± 10.3	3.2	*5.87*	*42%*[f]	6.59 ± 1.39	-
12a	CN	H	1.9 ± 1.1	36.3 ± 16.0	19	*3.79*	2,790 ± 152	1.65 ± 0.29	216
12b	CN	2-F	12.6 ± 5.6	88.9 ± 4.5	7.1	*3.93*	256 ± 29	0.15 ± 0.03	217
12c	CN	2-Cl	72.4 ± 35.4	130 ± 29	1.8	*4.39*	44.4 ± 3.8	0.05 ± 0.02	106
12d	CN	2-Me	4.8 ± 1.9	64.7 ± 15.1	13	*4.30*	950 ± 52	0.48 ± 0.23	253
12e	CN	3-F	3.5 ± 1.5	32.1 ± 5.3	9.3	*3.93*	1,820 ± 433	0.91 ± 0.24	256
12f	CN	3-Cl	1.9 ± 0.6	31.7 ± 11.6	17	*4.39*	*7%*[f]	11.6 ± 1.8	-
12g	CN	3-Me	0.7 ± 0.2	11.2 ± 1.2	16	*4.30*	*2%*[f]	10.7 ± 3.9	-
13	CH_2CN	H	4.4 ± 2.5	16.3 ± 4.8	3.7	*3.72*	635 ± 57	3.05 ± 0.17	27

[a]Relative binding affinity (RBA) values were calculated by IC_{50}[**E2**]/IC_{50}[test compound] × 100 (RBA of **E2** = 100), shown as mean ± SD of three or four independent experiments, performed in duplicate.

[b]β/α values = ERβ-RBA/ERα-RBA (ERβ selectivity of binding affinity).

[c]Log *P* values were calculated using Marvin 6. 2. 0 (ChemAxon).

[d]EC_{50} values are shown as Mean ± SD of three independent experiments, performed in duplicate.

[e]Rel.β/α values = {ERβ-EC_{50}[**E2**]/ERβ-EC_{50}[compound]}/{ERα-EC_{50}[**E2**]/ERα-EC_{50}[compound]} (ERβ

selectivity of agonistic activity).

[f]The value is the reporter activation at 3 μM, normalized by the maximum response of **E2**, which is set as 100%

In contrast, introduction of a methyl group on the indane-1-position enhanced the binding affinity for ERβ with a slight loss of selectivity (**7a** vs **11a**), and this result prompted us to examine the effects of the alkyl chain length. Increasing the size of the alkyl substituent at the indane-1-position from methyl to ethyl (**11b**) and propyl (**11c**) maintained a high RBA for ERβ however at the expense of selectivity. Further extension to butyl (**11d**) caused reduction of the RBA values on both ERs. This difference in substituent effects on ERs was probably due to the slight difference in the cavity size around this position. In addition to the spatial acceptance of alkyl substitution at this position, the pharmacophore model constructed from indazole-type ligands[33] suggested that analogues substituted with polar or polarizable groups instead of alkyl groups could result in a more selective ERβ ligand, and therefore we next examined 1-cyano derivative **12a** and its homologue **13**.

As expected, introduction of a nitrile group resulted in an improvement in ERβ selectivity due to the marked loss of ERα affinity. Cyanide **12a** showed improved

selectivity for ERβ compared to unsubstituted indane **7a**, even though its ERβ affinity was lowered. High ERβ selectivities of some nitrile-containing ligands are explained by a slight difference in interactions of the nitrile group with two non-conserved residues in the LBP of ERs, Leu384 (ERα)/Met336 (ERβ) and Met421 (ERα)/Ile373 (ERβ). The nitrile in WAY-292 **3b** is thought to cause a repulsive interaction with Met421 (ERα) and show a greater increase in binding affinity for ERβ by dispersive and inductive interactions with Leu373 (ERβ).[34] Alternatively, a modeling study of DPN **5c** shows that a productive interaction of nitrile with Met336 (ERβ) contributes to a more elevated affinity for ERβ.[35] In contrast to the improving effects of nitrile group in these ligands on ERβ affinities, the lower RBA of **12a** on ERβ compared to **7a** suggests that the role of the nitrile group of **12a** is different from the interactions with the ERs proposed above. In its homologue **13**, a significant decrease in the RBA for ERβ compared to **7a** was observed, suggesting that the cyanomethyl group might cause steric hindrance, similar to the butyl group of **11d**.

Of note, cyanide **12a** exhibits attractive ERβ selectivity and has a lower lipophilicity (calculated value: Log P = 3.79, approximately equal to that of endogenous ligand **E2**) than **7a** and other derivatives. Hence, **12a** and its analogues are likely a better probe to explore the in vivo effects of ERβ agonist.

Further SAR studies were conducted using **12a** as a second template and we examined substituent effects on the pendant phenyl group. Every 2-substituted derivatives **12b**–**d** exhibited higher RBAs to both ERs compared to **12a**, and a relative increase in ERα affinity resulted in a decrease in ERβ selectivity. In particular, the 2-chloro derivative **12c** showed superior affinity for ERβ compared to **E2**, but the subordinate increase in ERα affinity resulted in a higher loss of selectivity. These substituent effects on the pendant phenyl of **12a** are similar to those on A-ring of ring B seco-estradiol **6**,[36] in which the corresponding structure of the B-ring of **E2** is absent, suggesting that the pendant phenyl of **12a** may mimic the A-ring of **E2**. Computational docking studies of ring B seco-estradiols with ERα indicate that 5-chloro substitution of **6** could restore the hydrophobic interactions with neighboring residues of the B-ring of **E2**,[36] thus, the chlorine atom of **12c** likely contributes to the high RBA for ERα in the same manner described above.

On the other hand, substitution at the 3-position did not improve the ERβ affinity, but compounds **12e**–**g** showed higher selectivities for ERβ compared to the corresponding 2-substituted derivatives.

In this series of substituted phenols, compounds **12b**, **12d,** and **12e** exerted comparable or improved functional activities and selectivities for ERβ compared to **12a**,

unfortunately the agonistic activity of **12f** was weak. Because cell-based reporter gene assays are affected by various transcriptional co-regulators or cellular metabolism, unexpected factors might be involved in the differences between the two assay systems. Except for **12f**, the transcriptional activities of compounds listed in Table 2 were mostly correlated to their binding affinities.

Table 3. Binding affinities and transcriptional activities for ERs and ERβ selectivities of the enantiomers of **7a** and **12a**.

Ligand	RBA[a] (%)			Transcriptional acitivity EC_{50}[c] (nM)		
	hERα	hERβ	β/α[b]	hERα	hERβ	Rel.β/α[d]
***rac*-7a**	9.9 ± 3.6	67.8 ± 9.4	6.8	1,170 ± 265	1.14 ± 0.21	131
***R*-7a**	9.2 ± 2.5	44.8 ± 7.5	4.9	1,080 ± 89	1.40 ± 0.62	99
***S*-7a**	8.2 ± 2.8	59.7 ± 6.3	7.3	1,160 ± 131	1.28 ± 0.46	115
***rac*-12a**	1.9 ± 1.1	36.3 ± 16.0	19	2,790 ± 152	1.65 ± 0.29	216
***R*-12a**	1.9 ± 0.3	44.0 ± 21.9	24	2,410 ± 56	0.78 ± 0.12	394
***S*-12a**	1.5 ± 0.4	23.8 ± 6.2	16	3,020 ± 184	3.17 ± 0.88	122

[a]Relative binding affinity (RBA) values were calculated by IC_{50}[**E2**]/IC_{50}[test compound] × 100 (RBA of **E2** = 100), shown as mean ± SD of three or four

independent experiments, performed in duplicate.

[b]β/α values = ERβ-RBA/ERα-RBA (ERβ selectivity of binding affinity).

[c]EC_{50} values are shown as Mean ± SD of three independent experiments, performed in duplicate.

[d]Rel.β/α values = {ERβ-EC_{50}[**E2**]/ERβ-EC_{50}[compound]}/{ERα-EC_{50}[**E2**]/ERα-EC_{50}[compound]} (ERβ selectivity of agonistic activity).

The above SAR studies, employing readily available racemic mixtures, clarified the potential of the 1-benzylindane scaffold to afford highly potent and selective ERβ agonists comparable to isobutestrol **5b** and DPN **5c**. As such, we confirmed the pharmacological differences of the optical isomers. We prepared each enantiomer of the two template compounds **7a** and **12a**, and evaluated their properties on ERs; however, no improvement was observed with unsubstituted ***R*-7a** and ***S*-7a** compared to ***rac*-7a** (Table 3). The 1-cyano derivative ***R*-12a** showed higher binding affinity and agonistic activity for ERβ compared to ***rac*-12a** and ***S*-12a**, and its ERβ selectivities were also improved in both assays. The enantiomers of DPN **5c** show the same degree of action for ERs, likely due to the high flexibility of the molecule.[37] In contrast, SERBA-1 **4**

having a rigid fused-ring, is superior to the opposite enantiomer.[22] These findings suggest that structural flexibility of the ligand molecule might influence stereo-recognition by ERs. Therefore, the nitrile group in the indane-1-position could be considered to have an effect on increasing the rigidness of the molecule.

4. Modeling Study

To rationalize the high ERβ selectivity of ***R*-12a**, we conducted molecular modeling of this compound based on the X-ray crystal structure complex of ERB-041 **3a** with ERβ.[34] Fig. 3 shows the most suitable conformation of ***R*-12a** within the ERβ-LBP docked by FRED program (Open-Eye).

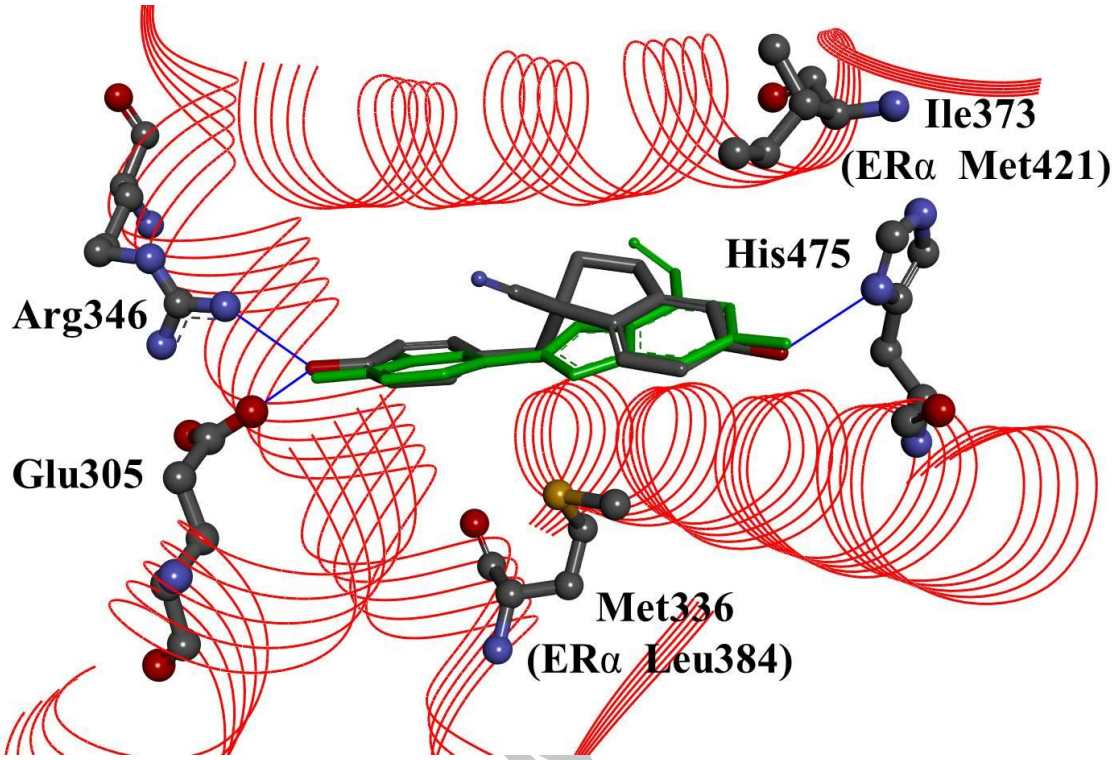


Figure 3. The most likely binding conformation of ***R*-12a** (stick, colored by element) docked into the ligand binding cavity of ERβ (red line ribbons) complexed with ERB-041 **3a** (green stick). Only key residues are displayed for simplicity (ball and stick, colored by element). Potential hydrogen bonds to key residues are shown as blue lines.

Consistent with our expectations, the two hydroxy groups are positioned at the two important hydrogen-bonding sites, and the hydroxy group on pendant phenyl ring is facing toward the Glu-Arg-water triad. The nitrile of ***R*-12a** is located in close proximity to the side chain of Leu298 (not shown in Fig. 3). In addition, it is projected onto the α-face of the cavity opposite to that of DPN **5c**,[35] and the position of this group is also

different from that of WAY-292 **3b**.[34] This observation is consistent with our SAR studies in which the influence of nitrile group on ERβ activity was different from DPN **5c** and WAY-292 **3b**. Although the role of the nitrile of ***R*-12a** on an improvement in ERβ selectivity is not well-defined, the linear geometry of the nitrile functionality might contribute to hold a preferred binding position for ERβ selectivity.

Interestingly, the ethylene moiety comprising the indane 2- and 3-positions was expected to overlap with the vinyl group of ERB-041 **3a** that interacts with Met421 (ERα)/Ile373 (ERβ), one of two non-conserved residues in LBP of ERs. Thus, we speculated that the 5-membered ring of indane caused an unfavorable interaction with Met421 (ERα) that contributed to the high ERβ selectivities of **7a** and **12a**. Furthermore, the indane was likely immobilized by the introduction of the 1-nitrile substituent and, consequently, the extremely high ERβ selectivity of ***R*-12a** was achieved.

5. Conclusions

In this study, we initially identified that 1-benzylindane derivative **7a** was an ERβ agonist with the possibility of a novel ERβ selective scaffold. We next carried out SAR studies using **7a** to confirm the optimal positions of two hydroxy groups and the suitable size of the bicyclic ring, and investigated substituent effects on the linker

between the two phenyl rings, leading to the more selective cyanide **12a**. Subsequent modifications of the pendant phenyl ring of **12a** also improved the properties and afforded more promising ERβ selective agonists **12b**, **12d**, and **12e**. We also prepared each enantiomer of the representative templates **7a** and **12a**, and the (*R*)-isomer of **12a** showed an improved profile compared to the racemic mixture, comparable to structurally related DPN **5c**. These findings suggested that this indane-based scaffold has comparable potential to provide various attractive ERβ agonistic probes with other multiple nonsteroidal ERβ ligands.

Further derivatization of this series of compounds and investigation of their in vivo pharmacology will appear in due course.

6. Experimental

6.1. Chemistry

All reagents and solvents were purchased from commercial sources and used without further purification. All moisture and air sensitive reactions were carried out under an argon atmosphere. Reactions were monitored by thin layer chromatography (TLC) using Merck Kieselgel 60 F_{254} plates or Fuji Silysia Chemical Ltd. Chromatorex NH-TLC plates. Flash column chromatography was performed on Biotage prepacked

columns using an automated flash chromatography system (Biotage, Isolera One). Melting points were determined on a Yanaco micro melting point apparatus (MP-J3). ^{1}H NMR spectra were recorded on a Bruker AV400M spectrometer at 400.1 MHz. Chemical shifts (δ) are reported in parts per million (ppm) units using tetramethylsilane as an internal standard. Data are presented as follows; chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet; br, broad; br s, broad singlet), coupling constant, and integration. ^{13}C NMR spectra were recorded on a Bruker AV400M spectrometer at 100.6 MHz with complete proton decoupling. Chemical shifts (δ) are reported in parts per million (ppm) with the solvent as the internal reference (δ 77.16 in $CDCl_3$ or δ 39.52 in DMSO-d_6).[38] High resolution mass spectra (HRMS) were recorded on an Agilent Technologies 6520 Accurate-Mass Q-TOF instrument using electrospray ionization (ESI, positive or negative ion mode). The chemical purity and optical purity of tested compounds were determined by HPLC–UV analysis, which was performed on a Shimadzu LC-VP series instrument (conditions and chromatograms are shown in supplemental data). Optical rotations were recorded on a HORIBA SEPA-300 using a 3.5 mm × 50 mm cell. Data are presented as follows; specific rotation, concentration (*c* = g/100 mL), and solvent.

6.1.1. (5-Methoxy-2,3-dihydro-1*H*-inden-1-yl)(4-methoxyphenyl)methanone (**15a**)

To a mixture of 5-methoxy-2,3-dihydro-1*H*-indene-1-carboxylic acid **14** (2.31 g, 12.0 mmol), *N*,*O*-dimethylhydroxylamine hydrochloride (2.34 g, 24.0 mmol), 1-hydroxybenzotriazole monohydrate (HOBt·H_2O) (2.21 g, 14.4 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI·HCl) (3.45 g, 18.0 mmol) in dichloromethane (DCM) (60 mL) was added dropwise Et_3N (1.82 g, 18.0 mmol) under ice cooling, and the mixture was stirred at room temperature overnight. The reaction mixture was poured into water, and the resulting mixture was extracted with EtOAc. The extract was washed successively with water, saturated aqueous $NaHCO_3$ solution, and brine, and then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (gradient: 20–50% EtOAc in hexane) to give *N*,5-dimethoxy-*N*-methyl-2,3-dihydro-1*H*-indene-1-carboxamide (2.44 g, 86%). This intermediate (2.35 g, 10.0 mmol) was dissolved in tetrahydrofuran (THF) (30 mL). To the solution was added dropwise 4-methoxyphenyl magnesium bromide (0.5 M in THF, 50 mL, 25.0 mmol) under ice cooling, and the mixture was stirred at room temperature for 2 h. After addition of saturated aqueous NH_4Cl solution, the mixture was extracted with EtOAc. The extract was washed with water and brine, dried over anhydrous

Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by flash column chromatography on NH silica gel (gradient: 15–30% EtOAc in hexane) to give **15a** (1.84 g, 65%) as a white solid (mp 95–97 °C). ^{1}H NMR ($CDCl_3$) δ 2.36–2.56 (m, 2H), 2.92–3.02 (m, 1H), 3.08–3.18 (m, 1H), 3.77 (s, 3H), 3.90 (s, 3H), 4.90–4.97 (m, 1H), 6.65 (dd, *J* = 2.5, 8.3 Hz, 1H), 6.82 (d, *J* = 2.5 Hz, 1H), 6.95 (d, *J* = 8.3 Hz, 1H), 6.96–7.02 (m, 2H), 8.01–8.08 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 30.1, 32.4, 51.5, 55.5, 55.7, 110.2, 112.5, 114.0, 125.6, 130.1, 131.3, 134.1, 146.4, 159.5, 163.7, 199.3; HRMS calcd for $C_{18}H_{19}O_3$ $(M + H)^+$ 283.1329, found 283.1320.

6.1.2. (5-Methoxy-2,3-dihydro-1*H*-inden-1-yl)(3-methoxyphenyl)methanone (**15b**)

The title compound was prepared as described for the synthesis of **15a**, using 3-methoxyphenyl magnesium bromide (1 M in THF) instead of 4-methoxyphenyl magnesium bromide (0.5 M in THF), and obtained as a pale yellow oil in 76% yield. ^{1}H NMR ($CDCl_3$) δ 2.38–2.57 (m, 2H), 2.92–3.03 (m, 1H), 3.08–3.18 (m, 1H), 3.77 (s, 3H), 3.86 (s, 3H), 4.95 (dd, *J* = 6.5, 8.0 Hz, 1H), 6.66 (dd, *J* = 2.5, 8.2 Hz, 1H), 6.82 (d, *J* = 2.5 Hz, 1H), 6.96 (d, *J* = 8.2 Hz, 1H), 7.12–7.18 (m, 1H), 7.40–7.46 (m, 1H), 7.56 (dd, *J* = 1.5, 2.5 Hz, 1H), 7.63–7.68 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 30.1, 32.3, 51.9, 55.5, 55.6,

110.3, 112.5, 113.2, 119.8, 121.7, 125.7, 129.8, 133.6, 138.6, 146.4, 159.6, 160.1, 200.6; HRMS calcd for $C_{18}H_{19}O_3$ $(M + H)^+$ 283.1329, found 283.1321.

6.1.3. 1-(4-Hydroxybenzyl)-2,3-dihydro-1*H*-inden-5-ol (7a)[25]

To a suspension of **15a** (141 mg, 0.50 mmol) in trifluoroacetic acid (TFA) (1.2 mL) was added dropwise Et_3SiH (145 mg, 1.25 mmol) under ice cooling, and the mixture was stirred at the same temperature for 20 min. After stirring at room temperature for 1 h, 1 N aqueous NaOH solution (16 mL) was added dropwise to the mixture under ice cooling, and then the mixture was poured into water. The resulting mixture was extracted with EtOAc, and the extract was washed with saturated aqueous $NaHCO_3$ solution and brine. After drying over anhydrous Na_2SO_4, the solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (gradient: 5–20% EtOAc in hexane) to give 5-methoxy-1-(4-methoxybenzyl)-2,3-dihydro-1*H*-indene (122 mg, 91%). This intermediate (104 mg, 0.39 mmol) was dissolved in DCM (3.9 mL). The solution was cooled to −78 °C and BBr_3 (1 M in DCM, 1.16 mL, 1.16 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature over 6 h with stirring, and further stirred at room temperature for 2 h, before being diluted with EtOAc and

quenched by addition of crushed ice. The organic layer was separated, washed with water and brine, and then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (gradient: 20–40% EtOAc in hexane) to give **7a** (78 mg, 84%) as an off-white solid (mp 165–168 °C). ^{1}H NMR (DMSO-d_6) δ 1.56-1.67 (m, 1H), 1.92-2.02 (m, 1H), 2.44 (dd, *J* = 9.2, 13.5 Hz, 1H), 2.56-2.76 (m, 2H), 2.90 (dd, *J* = 5.5, 13.5 Hz, 1H), 3.13-3.23 (m, 1H), 6.50 (dd, *J* = 2.2, 8.1 Hz, 1H), 6.57 (d, *J* = 2.2 Hz, 1H), 6.63-6.69 (m, 2H), 6.88 (d, *J* = 8.1 Hz, 1H), 6.95-7.02 (m, 2H), 9.05 (br s, 1H), 9.14 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 30.7, 31.6, 40.3, 45.3, 111.1, 112.9, 114.9, 124.1, 129.8, 130.8, 136.9, 144.9, 155.4, 156.2; HRMS calcd for $C_{16}H_{17}O_2$ $(M + H)^+$ 241.1223, found 241.1222; calcd for $C_{16}H_{15}O_2$ $(M - H)^-$ 239.1078, found 239.1080; HPLC purity: 99.3% (retention time: t_R 17.2 min).

6.1.4. 1-(3-Hydroxybenzyl)-2,3-dihydro-1*H*-inden-5-ol (**7b**)

The title compound was prepared from **15b** as described for the synthesis of **7a**, and obtained as a pale pink solid (mp 141–143 °C) in 59% yield. ^{1}H NMR (DMSO-d_6) δ 1.56–1.68 (m, 1H), 1.93–2.04 (m, 1H), 2.45 (dd, *J* = 9.3, 13.4 Hz, 1H), 2.58–2.77 (m, 2H), 2.94 (dd, *J* = 5.5, 13.4 Hz, 1H), 3.13–3.27 (m, 1H), 6.50 (dd, *J* = 2.3, 8.1 Hz, 1H),

6.56–6.67 (m, 4H), 6.91 (d, J = 8.1 Hz, 1H), 7.06 (t, J = 7.8 Hz, 1H), 9.06 (s, 1H), 9.23 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 30.7, 31.8, 41.1, 44.9, 111.1, 112.8, 112.9, 115.8, 119.6, 124.0, 129.1, 136.8, 142.2, 144.9, 156.2, 157.2; HRMS calcd for $C_{16}H_{17}O_2$ $(M + H)^+$ 241.1223, found 241.1221; calcd for $C_{16}H_{15}O_2$ $(M - H)^-$ 239.1078, found 239.1081; HPLC purity: 95.7% (t_R 17.5 min).

6.1.5. 4-Methoxy-1-(4-methoxybenzyl)-2,3-dihydro-1*H*-indene (**19c**)

To a solution of 4-methoxy-1-indanone **16c** (162 mg, 1.00 mmol) in toluene (10 mL) was added dropwise 4-methoxybenzyl magnesium chloride (0.25 M in THF, 10 mL, 2.50 mmol) under ice cooling, and the mixture was stirred at room temperature for 2 h. After addition of saturated aqueous NH_4Cl solution, the reaction mixture was extracted with EtOAc. The extract was washed with brine, dried over anhydrous $MgSO_4$, and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (gradient: 10–30% EtOAc in hexane) to give 4-methoxy-1-(4-methoxybenzyl)-2,3-dihydro-1*H*-inden-1-ol (247 mg). This intermediate (247 mg) was dissolved in THF (3.0 mL) and MeOH (3.0 mL), and 10% Pd–C (52% wet with water, 50 mg) was added to the solution. The mixture was stirred under a hydrogen atmosphere at room temperature for 3 h. After removal of the

insoluble materials by filtration, the filtrate was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel (gradient: 0–15% EtOAc in hexane) to give **19c** (191 mg, 71%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.70–1.81 (m, 1H), 2.08–2.19 (m, 1H), 2.63 (dd, *J* = 9.3, 13.8 Hz, 1H), 2.67–2.77 (m, 1H), 2.85 (ddd, *J* = 5.2, 8.7, 16.0 Hz, 1H), 3.06 (dd, *J* = 5.7, 13.8 Hz, 1H), 3.36–3.46 (m, 1H), 3.80 (s, 3H), 3.83 (s, 3H), 6.69 (d, *J* = 8.3 Hz, 1H), 6.75 (d, *J* = 7.5 Hz, 1H), 6.81–6.87 (m, 2H), 7.09–7.17 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 27.7, 31.6, 40.7, 47.2, 55.3, 55.4, 108.2, 113.8, 116.4, 127.6, 130.1, 131.7, 133.1, 149.1, 156.1, 158.0; HRMS (ESI) calcd for $C_{18}H_{21}O_2$ $(M + H)^+$ 269.1536, found 269.1530.

6.1.6. 6-Methoxy-1-(4-methoxybenzyl)-2,3-dihydro-1*H*-indene (19d)

The title compound was prepared from **16d** as described for the synthesis of **19c**, and obtained as a colorless oil in 72% yield. ^{1}H NMR ($CDCl_3$) δ 1.71–1.82 (m, 1H), 2.09–2.19 (m, 1H), 2.64 (dd, *J* = 9.2, 13.7 Hz, 1H), 2.66–2.85 (m, 2H), 3.04 (dd, *J* = 5.9, 13.7 Hz, 1H), 3.31–3.40 (m, 1H), 3.75 (s, 3H), 3.80 (s, 3H), 6.65 (d, *J* = 2.3 Hz, 1H), 6.71 (dd, *J* = 2.3, 8.2 Hz, 1H), 6.82–6.88 (m, 2H), 7.08–7.16 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 30.4, 32.5, 40.5, 46.9, 55.4, 55.5, 109.6, 112.4, 113.8, 125.0, 130.1, 133.0, 136.2, 148.6, 158.0, 158.6; HRMS (ESI) calcd for $C_{18}H_{21}O_2$ $(M + H)^+$ 269.1536, found

269.1529.

6.1.7. 6-Methoxy-1-(4-methoxybenzyl)-1,2,3,4-tetrahydronaphthalene (20)[25]

The title compound was prepared from **17** as described for the synthesis of **19c**, and obtained as a colorless oil in 62% yield. ^{1}H NMR ($CDCl_3$) δ 1.55–1.72 (m, 3H), 1.79–1.91 (m, 1H), 2.57–2.83 (m, 3H), 2.92–3.05 (m, 2H), 3.78 (s, 3H), 3.81 (s, 3H), 6.63 (d, *J* = 2.8 Hz, 1H), 6.71 (dd, *J* = 2.8, 8.5 Hz, 1H), 6.82–6.88 (m, 2H), 7.03–7.15 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 19.4, 26.9, 30.2, 39.1, 42.7, 55.3, 55.4, 112.0, 113.6, 113.8, 129.9, 130.2, 133.0, 133.3, 138.4, 157.5, 158.0; HRMS (ESI) calcd for $C_{19}H_{23}O_2$ $(M + H)^+$ 283.1693, found 283.1689.

6.1.8. 2-Methoxy-5-(4-methoxybenzyl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene (21)

The title compound was prepared from **18** as described for the synthesis of **19c**, and obtained as a white solid (mp 78–80 °C) in 74% yield. ^{1}H NMR ($CDCl_3$) δ 1.33–1.51 (br, 1H), 1.53–1.78 (m, 4H), 1.80–1.93 (m, 1H), 2.77–2.93 (m, 3H), 3.01–3.12 (m, 2H), 3.78 (s, 3H), 3.79 (s, 3H), 6.62 (dd, *J* = 2.8, 8.2 Hz, 1H), 6.69 (d, *J* = 2.8 Hz, 1H), 6.78–6.85 (m, 2H), 6.99 (d, *J* = 8.2 Hz, 1H), 7.04–7.11 (m, 2H); ^{13}C NMR

($CDCl_3$) δ 28.2, 29.0 (br s), 32.3, 36.5, 38.9, 45.6 (br s), 55.26, 55.33, 110.3, 113.7, 115.9, 128.2 (br s), 130.1, 133.6, 137.7, 144.1, 157.6, 157.8; HRMS (ESI) calcd for $C_{20}H_{25}O_2$ $(M + H)^+$ 297.1849, found 297.1840.

6.1.9. 1-(4-Hydroxybenzyl)-2,3-dihydro-1*H*-inden-4-ol (**7c**)

A solution of **19c** (134 mg, 0.50 mmol) in DCM (5.0 mL) was cooled to − 78 °C, and BBr_3 (1 M in DCM, 1.50 mL, 1.50 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature slowly, and further stirred at room temperature overnight, before being diluted with EtOAc and quenched by addition of crushed ice. The organic layer was separated, washed with water and brine, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (gradient: 20–40% EtOAc in hexane) to give **7c** (89 mg, 74%) as a pale yellow solid (mp 158–161 °C). ^{1}H NMR (DMSO-d_6) δ 1.55–1.68 (m, 1H), 1.90–2.02 (m, 1H), 2.40–2.62 (m, 2H), 2.64–2.75 (m, 1H), 2.94 (dd, *J* = 5.3, 13.6 Hz, 1H), 3.21–3.32 (m, 1H), 6.56 (d, *J* = 7.8 Hz, 1H), 6.60 (d, *J* = 7.3 Hz, 1H), 6.63–6.70 (m, 2H), 6.89–6.95 (m, 1H), 6.96–7.04 (m, 2H), 9.11 (s, 1H), 9.14 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 27.3, 30.9, 40.0, 46.5, 112.9, 114.5, 115.0, 127.2, 129.2, 129.8, 130.7, 148.8, 153.4, 155.4; HRMS (ESI) calcd for

$C_{16}H_{17}O_2$ $(M + H)^+$ 241.1223, found 241.1221; calcd for $C_{16}H_{15}O_2$ $(M - H)^-$ 239.1078, found 239.1080; HPLC purity: 94.3% (t_R 17.3 min).

6.1.10. 1-(4-Hydroxybenzyl)-2,3-dihydro-1*H*-inden-6-ol (7d)

The title compound was prepared from **19d** as described for the synthesis of **7c**, and obtained as a white solid (mp 116–119 °C) in 82% yield. ^{1}H NMR (DMSO-d_6) δ 1.56–1.68 (m, 1H), 1.91–2.02 (m, 1H), 2.45 (dd, *J* = 9.3, 13.6 Hz, 1H), 2.53–2.73 (m, 2H), 2.91 (dd, *J* = 5.5, 13.6 Hz, 1H), 3.16–3.27 (m, 1H), 6.52 (dd, *J* = 2.1, 7.9 Hz, 1H), 6.55 (d, *J* = 2.1 Hz, 1H), 6.64–6.71 (m, 2H), 6.95 (d, *J* = 7.9 Hz, 1H), 6.98–7.05 (m, 2H), 9.02 (s, 1H), 9.15 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 29.7, 31.8, 39.8, 46.2, 110.7, 113.4, 115.0, 124.6, 129.8, 130.7, 133.5, 148.2, 155.4, 155.9; HRMS (ESI) calcd for $C_{16}H_{17}O_2$ $(M + H)^+$ 241.1223, found 241.1215; calcd for $C_{16}H_{15}O_2$ $(M - H)^-$ 239.1078, found 239.1081; HPLC purity: 98.3% (t_R 17.8 min).

6.1.11. 5-(4-Hydroxybenzyl)-5,6,7,8-tetrahydronaphthalen-2-ol (8)[25]

The title compound was prepared from **20** as described for the synthesis of **7c**, and obtained as a white solid (mp 134–136 °C) in 81% yield. ^{1}H NMR (DMSO-d_6) δ 1.40–1.60 (m, 3H), 1.66–1.82 (m, 1H), 2.40–2.50 (m, 1H), 2.55–2.70 (m, 2H),

2.75–2.90 (m, 2H), 6.43 (d, *J* = 2.5 Hz, 1H), 6.51 (dd, *J* = 2.5, 8.3 Hz, 1H), 6.64–6.71 (m, 2H), 6.96–7.06 (m, 3H), 9.01 (s, 1H), 9.15 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 18.8, 26.2, 29.4, 38.4, 42.2, 113.1, 114.8, 115.0, 129.6, 130.0, 130.7, 130.9, 137.4, 154.9, 155.4; HRMS (ESI) calcd for $C_{17}H_{19}O_2$ $(M + H)^+$ 255.1380, found 255.1375; calcd for $C_{17}H_{17}O_2$ $(M - H)^-$ 253.1234, found 253.1235; HPLC purity: 97.7% (t_R 17.9 min).

6.1.12. 5-(4-Hydroxybenzyl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-2-ol (**9**)

The title compound was prepared from **21** as described for the synthesis of **7c**, and obtained as a white solid (mp 169–172 °C) in 90% yield. ^{1}H NMR (DMSO-d_6) δ 1.15–1.39 (br, 1H), 1.41–1.69 (m, 4H), 1.71–1.87 (m, 1H), 2.65–2.81 (m, 3H), 2.88 (dd, *J* = 6.2, 13.4 Hz, 1H), 2.94–3.04 (m, 1H), 6.43 (dd, *J* = 2.6, 8.1 Hz, 1H), 6.50 (d, *J* = 2.6 Hz, 1H), 6.60–6.67 (m, 2H), 6.84 (d, *J* = 8.1 Hz, 1H), 6.94–7.01 (m, 2H), 9.00 (s, 1H), 9.11 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 27.9, 28.4 (br s), 32.1, 35.6, 38.3, 44.7 (br s), 112.0, 115.00, 116.6, 128.0 (br s), 129.8, 131.2, 135.4, 143.2, 155.0, 155.3; HRMS (ESI) calcd for $C_{18}H_{21}O_2$ $(M + H)^+$ 269.1536, found 269.1531; calcd for $C_{18}H_{19}O_2$ $(M - H)^-$ 267.1391, found 267.1392; HPLC purity: 99.5% (t_R 19.1 min).

6.1.13. 5-Methoxy-1-[1-(4-methoxyphenyl)propyl]-2,3-dihydro-1*H*-indene (**22**)

To a suspension of ethyltriphenylphosphonium bromide (653 mg, 1.76 mmol) in THF (3.3 mL) was added dropwise *n*-BuLi (2.66 M in Hex, 0.62 mL, 1.65 mmol) under ice-cooling, and the mixture was stirred at the same temperature for 10 min. After stirring at room temperature for 30 min, a solution of **15a** (311 mg, 1.10 mmol) in THF (3.3 mL) was added to the mixture under ice-cooling, and the mixture was stirred at room temperature for 1.5 days. The reaction mixture was poured into saturated aqueous NH_4Cl solution, and extracted with EtOAc. The extract was washed with water and brine, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (gradient: 5–10% EtOAc in hexane) to give 5-methoxy-1-[1-(4-methoxyphenyl)prop-1-en-1-yl]-2,3-dihydro-1*H*-indene (70 mg, 22%). The suspension of this intermediate (70 mg) and 10% Pd–C (52% wet with water, 14 mg) in THF (2.3 mL) and MeOH (2.3 mL) was stirred under a hydrogen atmosphere at room temperature for 3 h. After removal of the insoluble materials by filtration, the filtrate was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel (gradient: 0–10% EtOAc in hexane) to give **22** (55 mg, 78%) as a colorless oil (58/42 diastereomixture, determined by NMR spectrum). ^{1}H NMR ($CDCl_3$) major diastereomer: δ 0.73 (t, J = 7.3 Hz, 3H), 1.58–1.80 (m, 2H),

1.83–2.04 (m, 2H), 2.47–2.65 (m, 3H), 3.19–3.28 (m, 1H), 3.782 (s, 3H), 3.783 (s, 3H), 6.67–6.75 (m, 2H), 6.76–6.84 (m, 2H), 6.96–7.03 (m, 2H), 7.20 (d, *J* = 7.8 Hz, 1H); minor diastereomer: δ 0.74 (t, *J* = 7.3 Hz, 3H), 1.56–2.03 (m, 3H), 2.17–2.29 (m, 1H), 2.55–2.71 (m, 3H), 3.29–3.37 (m, 1H), 3.75 (s, 3H), 3.81 (s, 3H), 6.54 (dd, *J* = 2.4, 8.4 Hz, 1H), 6.57 (d, *J* = 8.4 Hz, 1H), 6.67–6.75 (m, 1H), 6.76–6.84 (m, 2H), 6.96–7.03 (m, 2H); ^{13}C NMR ($CDCl_3$) major diastereomer: δ 12.5, 26.8, 30.2, 31.3, 50.1, 50.7, 55.3, 55.5, 109.9, 111.6, 113.4, 126.1, 129.5, 136.0, 138.8, 146.5, 157.8, 158.8; minor diastereomer: δ 12.4, 26.1, 30.8, 31.6, 50.0, 51.9, 55.3, 55.4, 109.7, 111.5, 113.5, 125.5, 129.6, 136.4, 138.1, 146.6, 158.0, 158.7; HRMS (ESI) calcd for $C_{20}H_{25}O_2$ $(M + H)^+$ 297.1849, found 297.1844.

6.1.14. 1-[1-(4-Hydroxyphenyl)propyl]-2,3-dihydro-1*H*-inden-5-ol (10)

The title compound was prepared from **22** as described for the synthesis of **7c**, and obtained as a pale yellow foam in 84% yield. ^{1}H NMR (DMSO-d_6) major diastereomer: δ 0.65 (t, *J* = 7.3 Hz, 3H), 1.45–1.90 (m, 4H), 2.38–2.55 (m, 3H), 3.05–3.15 (m, 1H), 6.48–6.55 (m, 2H), 6.58–6.67 (m, 2H), 6.84–6.92 (m, 2H), 7.07 (d, *J* = 8.0 Hz, 1H), 9.04 (s, 1H), 9.09 (s, 1H); minor diastereomer: δ 0.65 (t, *J* = 7.3 Hz, 3H), 1.45–1.90 (m, 3H), 2.01–2.13 (m, 1H), 2.38–2.55 (m, 3H), 3.15–3.23 (m, 1H),

6.35 (dd, J = 2.3, 8.1 Hz, 1H), 6.44 (d, J = 8.1 Hz, 1H), 6.48–6.55 (m, 1H), 6.58–6.67 (m, 2H), 6.84–6.92 (m, 2H), 9.00 (s, 1H), 9.14 (s, 1H); ^{13}C NMR (DMSO-d_6) major diastereomer: δ 12.3, 26.1, 29.4, 30.5, 49.4, 49.6, 111.1, 112.6, 114.7, 125.7, 129.2, 133.5, 136.3, 145.5, 155.3, 156.1; minor diastereomer: δ 12.2, 25.2, 30.1, 30.9, 49.3, 51.0, 110.9, 112.6, 114.8, 124.9, 129.1, 134.0, 135.7, 145.7, 155.4, 156.0; HRMS (ESI) calcd for $C_{18}H_{21}O_2$ $(M + H)^+$ 269.1536, found 269.1535; calcd for $C_{18}H_{19}O_2$ $(M - H)^-$ 267.1391, found 267.1394; HPLC purity: 55.0% (t_R 19.4 min), 40.3% (t_R 19.9 min).

6.1.15. 5-Methoxy-1-methyl-2,3-dihydro-1*H*-indene-1-carbaldehyde (**24a**)

To a solution of 5-methoxy-2,3-dihydro-1*H*-indene-1-carbonitrile **23** (260 mg, 1.50 mmol) and iodomethane (426 mg, 3.00 mmol) in DMF (4.5 mL) was added NaH (72 mg, 1.80 mmol, 60% oil dispersion) in small portions under ice-cooling, and the mixture was stirred at the same temperature for 30 min. After stirring at room temperature overnight, saturated aqueous NH_4Cl solution was added, and the resulting mixture was extracted with Et_2O. The extract was washed with water and brine, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (gradient: 5–15% EtOAc in hexane) to give 5-methoxy-1-methyl-2,3-dihydro-1*H*-indene-1-carbonitrile (257 mg,

92%). This intermediate (225 mg, 1.20 mmol) was dissolved in toluene (4.8 mL). Diisobutylaluminum hydride (DIBAL-H) (1.03 M in Hexane, 1.28 mL, 1.32 mmol) was added dropwise to the solution at −78 °C, and the mixture was stirred at the same temperature for 1 h. After addition of 2 N HCl (5 mL), the resulting mixture was stirred at room temperature overnight, poured into water, and then extracted with EtOAc. The extract was washed with water and brine, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (gradient: 5–15% EtOAc in hexane) to give **24a** (210 mg, 92%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.39 (s, 3H), 1.88–1.93 (m, 1H), 2.54–2.64 (m, 1H), 2.95–3.02 (m, 2H), 3.80 (s, 3H), 6.75–6.84 (m, 2H), 7.03 (d, *J* = 8.3 Hz, 1H), 9.50 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.5, 31.0, 34.4, 55.6, 58.9, 110.6, 113.0, 124.7, 135.4, 146.4, 160.2, 201.4; HRMS (ESI) calcd for $C_{12}H_{15}O_2$ $(M + H)^+$ 191.1067, found 191.1065.

6.1.16. 1-Ethyl-5-methoxy-2,3-dihydro-1*H*-indene-1-carbaldehyde (**24b**)

The title compound was prepared as described for the synthesis of **24a**, using iodoethane instead of iodomethane, and obtained as a colorless oil in 76% yield. ^{1}H NMR ($CDCl_3$) δ 0.85 (t, *J* = 7.5 Hz, 3H), 1.69–1.80 (m, 1H), 1.91–2.08 (m, 2H),

2.53–2.63 (m, 1H), 2.90–2.97 (m, 2H), 3.79 (s, 3H), 6.75–6.82 (m, 2H), 7.06 (d, *J* = 8.0 Hz, 1H), 9.47–9.50 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 9.0, 27.2, 30.4, 31.1, 55.5, 63.5, 110.6, 112.8, 124.9, 133.9, 146.8, 160.2, 201.3; HRMS (ESI) calcd for $C_{13}H_{17}O_2$ $(M + H)^+$ 205.1223, found 205.1215.

6.1.17. 5-Methoxy-1-propyl-2,3-dihydro-1*H*-indene-1-carbaldehyde (**24c**)

The title compound was prepared as described for the synthesis of **24a**, using 1-iodopropane instead of iodomethane, and obtained as a colorless oil in 78% yield. ^{1}H NMR ($CDCl_3$) δ 0.92 (t, *J* = 7.3 Hz, 3H), 1.17–1.30 (m, 2H), 1.61–1.71 (m, 1H), 1.91–2.02 (m, 2H), 2.55–2.64 (m, 1H), 2.89–2.97 (m, 2H), 3.79 (s, 3H), 6.74–6.82 (m, 2H), 7.07 (d, *J* = 8.0 Hz, 1H), 9.46–9.50 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.8, 18.1, 31.0, 31.2, 37.0, 55.5, 63.2, 110.6, 112.8, 124.9, 134.2, 146.7, 160.1, 201.2; HRMS (ESI) calcd for $C_{14}H_{19}O_2$ $(M + H)^+$ 219.1380, found 219.1378.

6.1.18. 1-Butyl-5-methoxy-2,3-dihydro-1*H*-indene-1-carbaldehyde (**24d**)

The title compound was prepared as described for the synthesis of **24a**, using 1-iodobutane instead of iodomethane, and obtained as a colorless oil in 79% yield. ^{1}H NMR ($CDCl_3$) δ 0.88 (t, *J* = 7.3 Hz, 3H), 1.10–1.40 (m, 4H), 1.64–1.74 (m, 1H),

1.91–2.03 (m, 2H), 2.55–2.64 (m, 1H), 2.89–2.97 (m, 2H), 3.79 (s, 3H), 6.74–6.83 (m, 2H), 7.07 (d, J = 8.3 Hz, 1H), 9.46–9.49 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1, 23.4, 26.8, 31.0, 31.1, 34.4, 55.5, 63.1, 110.6, 112.8, 124.9, 134.2, 146.7, 160.1, 201.2; HRMS (ESI) calcd for $C_{15}H_{21}O_2$ $(M + H)^+$ 233.1536, found 233.1538.

6.1.19. 5-Methoxy-1-(4-methoxybenzyl)-1-methyl-2,3-dihydro-1*H*-indene (**25a**)

To a solution of 4-bromoanisole (122 mg 0.65 mmol) in THF (4.0 mL) was added dropwise *n*-BuLi (2.66 M in hexane, 0.23 mL, 0.61 mmol) at −78 °C, and the mixture was stirred at the same temperature for 15 min. A solution of **24a** (95 mg, 0.50 mmol) in THF (1.0 mL) was added dropwise to the mixture, and the mixture was stirred at the same temperature for 30 min, and then at room temperature for 1 h. After addition of saturated aqueous NH_4Cl solution, the reaction mixture was extracted with EtOAc. The extract was washed with brine, dried over anhydrous $MgSO_4$, and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (gradient: 15–20% EtOAc in hexane) to give (5-methoxy-1-methyl-2,3-dihydro-1*H*-inden-1-yl)(4-methoxyphenyl)methanol (143 mg). The suspension of this intermediate (143 mg) and 10% Pd–C (52% wet with water, 30 mg) in THF (1.5 mL) and MeOH (1.5 mL) was stirred under a hydrogen atmosphere at

room temperature for 3 h. After removal of the insoluble materials by filtration, the filtrate was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel (gradient: 3–10% EtOAc in hexane) to give **25a** (81 mg, 57%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.25 (s, 3H), 1.72–1.83 (m, 1H), 2.04–2.15 (m, 1H), 2.47–2.59 (m, 1H), 2.65–2.76 (m, 3H), 3.77 (s, 3H), 3.78 (s, 3H), 6.67–6.76 (m, 4H), 6.81–6.87 (m, 2H), 6.89 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 27.1, 30.4, 39.0, 47.0, 47.9, 55.3, 55.5, 109.8, 112.0, 113.1, 123.7, 131.38, 131.43, 143.1, 145.3, 158.0, 158.8; HRMS (ESI) calcd for $C_{19}H_{23}O_2$ $(M + H)^+$ 283.1693, found 283.1691.

6.1.20. 1-Ethyl-5-methoxy-1-(4-methoxybenzyl)-2,3-dihydro-1*H*-indene (25b)

The title compound was prepared from **24b** as described for the synthesis of **25a**, and obtained as a colorless oil in 72% yield. ^{1}H NMR ($CDCl_3$) δ 0.84 (t, *J* = 7.4 Hz, 3H), 1.55–1.74 (m, 2H), 1.83–2.04 (m, 2H), 2.37–2.48 (m, 1H), 2.61–2.74 (m, 2H), 2.76 (d, *J* = 13.3 Hz, 1H), 3.76 (s, 3H), 3.78 (s, 3H), 6.64–6.73 (m, 4H), 6.74–6.81 (m, 2H), 6.82 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 9.1, 30.6, 31.5, 35.5, 45.0, 51.9, 55.3, 55.4, 109.5, 111.9, 113.0, 124.5, 131.3, 131.4, 141.2, 146.0, 157.9, 158.8; HRMS (ESI) calcd for $C_{20}H_{25}O_2$ $(M + H)^+$ 297.1849, found 297.1846.

6.1.21. 5-Methoxy-1-(4-methoxybenzyl)-1-propyl-2,3-dihydro-1*H*-indene (25c)

The title compound was prepared from **24c** as described for the synthesis of **25a**, and obtained as a colorless oil in 81% yield. ^{1}H NMR ($CDCl_3$) δ 0.88 (t, *J* = 7.3 Hz, 3H), 1.12–1.41 (m, 2H), 1.45–1.56 (m, 1H), 1.57–1.68 (m, 1H), 1.83–1.94 (m, 1H), 1.95–2.06 (m, 1H), 2.36–2.49 (m, 1H), 2.61–2.75 (m, 2H), 2.77 (d, *J* = 13.1 Hz, 1H), 3.76 (s, 3H), 3.78 (s, 3H), 6.64–6.73 (m, 4H), 6.74–6.81 (m, 2H), 6.83 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 15.0, 18.0, 30.7, 36.1, 41.8, 45.4, 51.6, 55.3, 55.4, 109.5, 111.9, 113.0, 124.5, 131.3, 131.4, 141.5, 145.8, 157.9, 158.8; HRMS (ESI) calcd for $C_{21}H_{27}O_2$ $(M + H)^+$ 311.2006, found 311.2001.

6.1.22. 1-Butyl-5-methoxy-1-(4-methoxybenzyl)-2,3-dihydro-1*H*-indene (25d)

The title compound was prepared from **24d** as described for the synthesis of **25a**, and obtained as a colorless oil in 42% yield. ^{1}H NMR ($CDCl_3$) δ 0.87 (t, *J* = 7.2 Hz, 3H), 1.08–1.37 (m, 4H), 1.47–1.58 (m, 1H), 1.59–1.70 (m, 1H), 1.84–1.94 (m, 1H), 1.95–2.05 (m, 1H), 2.35–2.47 (m, 1H), 2.61–2.70 (m, 1H), 2.71 (d, *J* = 13.3 Hz, 1H), 2.76 (d, *J* = 13.3 Hz, 1H), 3.76 (s, 3H), 3.78 (s, 3H), 6.64–6.73 (m, 4H), 6.74–6.80 (m, 2H), 6.82 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.3, 23.6, 27.0, 30.7, 36.1, 39.1,

45.4, 51.5, 55.3, 55.4, 109.5, 111.9, 113.0, 124.5, 131.3, 131.4, 141.5, 145.8, 157.9, 158.8; HRMS (ESI) calcd for $C_{22}H_{29}O_2$ $(M + H)^+$ 325.2162, found 325.2158.

6.1.23. 1-(4-Hydroxybenzyl)-1-methyl-2,3-dihydro-1*H*-inden-5-ol (11a)

The title compound was prepared from **25a** as described for the synthesis of **7c**, and obtained as an off-white foam in 82% yield. ^{1}H NMR (DMSO-d_6) δ 1.14 (s, 3H), 1.53–1.65 (m, 1H), 1.96–2.07 (m, 1H), 2.33–2.45 (m, 1H), 2.52–2.64 (m, 3H), 6.49 (d, J = 1.8 Hz, 1H), 6.51–6.60 (m, 3H), 6.70–6.77 (m, 2H), 6.85 (d, J = 8.3 Hz, 1H), 9.03 (s, 1H), 9.11 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 27.1, 29.6, 38.0, 46.3, 47.2, 110.9, 113.0, 114.4, 123.2, 129.1, 131.0, 141.0, 144.3, 155.4, 156.1; HRMS (ESI) calcd for $C_{17}H_{19}O_2$ $(M + H)^+$ 255.1380, found 255.1375; calcd for $C_{17}H_{17}O_2$ $(M - H)^-$ 253.1234, found 253.1235; HPLC purity: 98.4% (t_R 18.5 min).

6.1.24. 1-Ethyl-1-(4-hydroxybenzyl)-2,3-dihydro-1*H*-inden-5-ol (11b)

The title compound was prepared from **25b** as described for the synthesis of **7c**, and obtained as an off-white foam in 81% yield. ^{1}H NMR (DMSO-d_6) δ 0.75 (t, J = 7.4 Hz, 3H), 1.45–1.61 (m, 2H), 1.66–1.77 (m, 1H), 1.85–1.96 (m, 1H), 2.22–2.34 (m, 1H), 2.50–2.62 (m, 2H), 2.67 (d, J = 13.1 Hz, 1H), 6.46 (d, J = 2.0 Hz, 1H), 6.49–6.56 (m,

3H), 6.64–6.70 (m, 2H), 6.78 (d, J = 8.0 Hz, 1H), 9.02 (s, 1H), 9.08 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 8.9, 29.9, 31.2, 34.5, 44.6, 51.2, 110.9, 112.9, 114.3, 124.0, 128.9, 131.0, 138.8, 145.1, 155.3, 156.0; HRMS (ESI) calcd for $C_{18}H_{21}O_2$ $(M + H)^+$ 269.1536, found 269.1534; calcd for $C_{18}H_{19}O_2$ $(M - H)^-$ 267.1391, found 267.1396; HPLC purity: 96.7% (t_R 19.7 min).

6.1.25. 1-(4-Hydroxybenzyl)-1-propyl-2,3-dihydro-1*H*-inden-5-ol (**11c**)

The title compound was prepared from **25c** as described for the synthesis of **7c**, and obtained as an off-white foam in 74% yield. ^{1}H NMR (DMSO-d_6) δ 0.82 (t, J = 7.3 Hz, 3H), 1.03–1.31 (m, 2H), 1.35–1.56 (m, 2H), 1.66–1.78 (m, 1H), 1.86–1.98 (m, 1H), 2.22–2.35 (m, 1H), 2.50–2.63 (m, 2H), 2.67 (d, J = 13.1 Hz, 1H), 6.46 (d, J = 2.0 Hz, 1H), 6.49–6.57 (m, 3H), 6.63–6.70 (m, 2H), 6.79 (d, J = 8.3 Hz, 1H), 9.01 (s, 1H), 9.08 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 14.8, 17.4, 29.9, 35.2, 41.6, 44.9, 50.9, 110.8, 112.9, 114.3, 123.9, 128.9, 131.0, 139.2, 144.9, 155.3, 156.0; HRMS (ESI) calcd for $C_{19}H_{23}O_2$ $(M + H)^+$ 283.1693, found 283.1689; calcd for $C_{19}H_{21}O_2$ $(M - H)^-$ 281.1547, found 281.1552; HPLC purity: 95.9% (t_R 21.0 min).

6.1.26. 1-Butyl-1-(4-hydroxybenzyl)-2,3-dihydro-1*H*-inden-5-ol (**11d**)

The title compound was prepared from **25d** as described for the synthesis of **7c**, and obtained as an off-white foam in 92% yield. ^{1}H NMR (DMSO-d_6) δ 0.82 (t, J = 7.0 Hz, 3H), 1.01–1.28 (m, 4H), 1.37–1.58 (m, 2H), 1.66–1.78 (m, 1H), 1.86–1.97 (m, 1H), 2.20–2.35 (m, 1H), 2.50–2.62 (m, 2H), 2.67 (d, J = 13.3 Hz, 1H), 6.45 (d, J = 2.0 Hz, 1H), 6.49–6.56 (m, 3H), 6.62–6.69 (m, 2H), 6.79 (d, J = 8.0 Hz, 1H), 9.01 (s, 1H), 9.08 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 14.1, 23.0, 26.4, 29.9, 35.1, 38.8, 45.0, 50.8, 110.8, 112.9, 114.3, 123.9, 128.9, 131.0, 139.2, 144.9, 155.3, 156.0; HRMS (ESI) calcd for $C_{20}H_{25}O_2$ $(M + H)^+$ 297.1849, found 297.1846; calcd for $C_{20}H_{23}O_2$ $(M - H)^-$ 295.1704, found 295.1703; HPLC purity: 97.4% (t_R 22.1 min).

6.1.27. 5-Methoxy-1-(4-methoxybenzyl)-2,3-dihydro-1*H*-indene-1-carbonitrile (**27a**)

To a solution of **23** (866 mg, 5.0 mmol) in THF (15.0 mL) was added dropwise lithium diisopropylamide (LDA) (1.13 M in THF and hexane, 5.3 mL, 6.0 mmol) at − 78 °C, and the mixture was stirred at the same temperature for 15 min. A solution of 4-methoxybenzyl chloride **26a** (1.02 g, 6.5 mmol) in THF (5.0 mL) was added dropwise to the mixture, and the reaction mixture was stirred at the same temperature for 30 min, and then at room temperature for 2 hour. The reaction mixture was poured into aqueous NH_4Cl solution, and the resulting mixture was extracted with EtOAc. The extract was

washed with water and brine, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (gradient: 10–25% EtOAc in hexane) to give **27a** (797 mg, 54%) as a white solid (mp 118–120 °C). ^{1}H NMR ($CDCl_3$) δ 2.31–2.40 (m, 1H), 2.44–2.54 (m, 1H), 2.71–2.82 (m, 1H), 2.87–2.98 (m, 2H), 3.07 (d, *J* = 13.6 Hz, 1H), 3.80 (s, 6H), 6.73–6.78 (m, 2H), 6.79–6.85 (m, 2H), 7.01–7.08 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 30.3, 37.4, 43.9, 47.7, 55.4, 55.6, 110.2, 113.1, 113.8, 123.7, 125.1, 127.6, 131.4, 134.1, 144.5, 159.0, 160.5; HRMS (ESI) calcd for $C_{19}H_{23}N_2O_2$ $(M + NH_4)^+$ 311.1754, found 311.1753.

6.1.28.

1-(2-Fluoro-4-methoxybenzyl)-5-methoxy-2,3-dihydro-1*H*-indene-1-carbonitrile (27b)

The title compound was prepared as described for the synthesis of **27a**, using 2-fluoro-4-methoxybenzyl bromide **26b** instead of **26a**, and obtained as a white solid (mp 78–81 °C) in 95% yield. ^{1}H NMR ($CDCl_3$) δ 2.33–2.42 (m, 1H), 2.43–2.53 (m, 1H), 2.80–2.98 (m, 2H), 2.99 (d, *J* = 13.9 Hz, 1H), 3.12 (d, *J* = 13.9 Hz, 1H), 3.796 (s, 3H), 3.804 (s, 3H), 6.59 (dd, *J* = 2.6, 11.7 Hz, 1H), 6.63–6.68 (m, 1H), 6.74–6.81 (m, 2H),

7.11–7.19 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 30.3, 36.4, 37.3, 47.7, 55.6, 55.7, 101.5, 101.7, 109.99, 110.02, 110.3, 113.3, 114.6, 114.7, 123.5, 124.7, 132.55, 132.61, 134.1, 144.5, 160.4, 160.46, 160.54, 160.8, 163.3; HRMS (ESI) calcd for $C_{19}H_{22}FN_2O_2$ $(M + NH_4)^+$ 329.1660, found 329.1661.

6.1.29.

1-(2-Chloro-4-methoxybenzyl)-5-methoxy-2,3-dihydro-1*H*-indene-1-carbonitrile (**27c**)

The title compound was prepared as described for the synthesis of **27a**, using 2-chloro-4-methoxybenzyl bromide **26c** instead of **26a**, and obtained as a pale yellow oil in 84% yield. ^{1}H NMR ($CDCl_3$) δ 2.40–2.55 (m, 2H), 2.90–2.98 (m, 2H), 3.11 (d, *J* = 14.1 Hz, 1H), 3.27 (d, *J* = 14.1 Hz, 1H), 3.799 (s, 3H), 3.804 (s, 3H), 6.72–6.78 (m, 2H), 6.79 (dd, *J* = 2.8, 8.5 Hz, 1H), 6.89 (d, *J* = 2.8 Hz, 1H), 7.02–7.07 (m, 1H), 7.30 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 30.5, 37.3, 39.6, 47.8, 55.61, 55.63, 110.2, 113.1, 113.3, 114.9, 123.6, 124.8, 125.6, 132.5, 134.0, 135.9, 144.5, 159.5, 160.6; HRMS (ESI) calcd for $C_{19}H_{22}ClN_2O_2$ $(M + NH_4)^+$ 345.1364, found 345.1366.

6.1.30.

5-Methoxy-1-(4-methoxy-2-methylbenzyl)-2,3-dihydro-1*H*-indene-1-carbonitrile (27d)

The title compound was prepared as described for the synthesis of **27a**, using 4-methoxy-2-methylbenzyl chloride **26d** instead of **26a**, and obtained as an off-white solid (mp 86–89 °C) in 91% yield. ^{1}H NMR ($CDCl_3$) δ 1.86 (s, 3H), 2.37–2.46 (m, 1H), 2.55–2.65 (m, 1H), 2.88–3.02 (m, 3H), 3.08 (d, *J* = 13.8 Hz, 1H), 3.79 (s, 6H), 6.63 (d, *J* = 2.7 Hz, 1H), 6.67 (dd, *J* = 2.4, 8.5 Hz, 1H), 6.72 (dd, *J* = 2.7, 8.3 Hz, 1H), 6.76 (d, *J* = 2.4 Hz, 1H), 6.89 (d, *J* = 8.5 Hz, 1H), 7.21 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 19.8, 30.4, 38.4, 39.5, 47.8, 55.3, 55.6, 110.2, 111.2, 113.0, 116.0, 124.0, 125.4, 126.3, 132.0, 133.9, 139.0, 144.2, 158.7, 160.5; HRMS (ESI) calcd for $C_{20}H_{25}N_2O_2$ $(M + NH_4)^+$ 325.1911, found 325.1903.

6.1.31.

1-(3-Fluoro-4-methoxybenzyl)-5-methoxy-2,3-dihydro-1*H*-indene-1-carbonitrile (27e)

The title compound was prepared as described for the synthesis of **27a**, using 3-fluoro-4-methoxylbenzyl bromide **26e** instead of **26a**, and obtained as a white solid (mp 138–141 °C) in 91% yield. ^{1}H NMR ($CDCl_3$) δ 2.29–2.39 (m, 1H), 2.45–2.56 (m,

1H), 2.73–2.85 (m, 1H), 2.89–2.99 (m, 2H), 3.05 (d, *J* = 13.6 Hz, 1H), 3.80 (s, 3H), 3.89 (s, 3H), 6.74–6.84 (m, 3H), 6.85–6.93 (m, 2H), 7.01–7.07 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 30.3, 37.5, 43.7, 47.6, 55.6, 56.4, 110.3, 113.19, 113.24, 117.9, 118.1, 123.4, 125.0, 126.1, 126.2, 128.38, 128.44, 133.7, 144.4, 147.1, 147.2, 150.8, 153.2, 160.6; HRMS (ESI) calcd for $C_{19}H_{22}FN_2O_2$ $(M + NH_4)^+$ 329.1660, found 329.1661.

6.1.32.

1-(3-Chloro-4-methoxybenzyl)-5-methoxy-2,3-dihydro-1*H*-indene-1-carbonitrile

(**27f**)

The title compound was prepared as described for the synthesis of **27a**, using 3-chloro-4-methoxylbenzyl bromide **26f** instead of **26a**, and obtained as a white solid (mp 146–148 °C) in 89% yield. ^{1}H NMR ($CDCl_3$) δ 2.29–2.39 (m, 1H), 2.46–2.56 (m, 1H), 2.72–2.84 (m, 1H), 2.87–2.99 (m, 2H), 3.04 (d, *J* = 13.6 Hz, 1H), 3.81 (s, 3H), 3.90 (s, 3H), 6.74–6.80 (m, 2H), 6.83–6.89 (m, 1H), 7.02–7.09 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 30.3, 37.4, 43.5, 47.6, 55.6, 56.3, 110.3, 111.9, 113.2, 122.1, 123.4, 125.0, 128.6, 129.6, 132.0, 133.7, 144.4, 154.5, 160.6; HRMS (ESI) calcd for $C_{19}H_{22}ClN_2O_2$ $(M + NH_4)^+$ 345.1364, found 345.1359.

6.1.33.

5-Methoxy-1-(4-methoxy-3-methylbenzyl)-2,3-dihydro-1*H*-indene-1-carbonitrile (27g)

The title compound was prepared as described for the synthesis of **27a**, using 4-methoxyl-3-methylbenzyl chloride **26g** instead of **26a**, and obtained as a white solid (mp 119–122 °C) in 84% yield. ^{1}H NMR ($CDCl_3$) δ 2.17 (s, 3H), 2.31–2.40 (m, 1H), 2.42–2.52 (m, 1H), 2.72–2.83 (m, 1H), 2.85–2.97 (m, 2H), 3.05 (d, *J* = 13.6 Hz, 1H), 3.80 (s, 3H), 3.82 (s, 3H), 6.71–6.79 (m, 3H), 6.88 (d, *J* = 1.8 Hz, 1H), 6.95 (dd, *J* = 1.8, 8.3 Hz, 1H), 7.05–7.11 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 16.3, 30.3, 37.4, 43.9, 47.8, 55.4, 55.6, 109.8, 110.2, 113.1, 123.7, 125.1, 126.4, 127.2, 128.6, 132.7, 134.3, 144.5, 157.2, 160.5; HRMS (ESI) calcd for $C_{20}H_{25}N_2O_2$ $(M + NH_4)^+$ 325.1911, found 325.1907.

6.1.34. 5-Hydroxy-1-(4-hydroxybenzyl)-2,3-dihydro-1*H*-indene-1-carbonitrile (12a)

The title compound was prepared from **27a** as described for the synthesis of **7c**, and obtained as a white solid (mp 184–188 °C) in 76% yield. ^{1}H NMR (DMSO-d_6) δ 2.18–2.35 (m, 2H), 2.65–2.87 (m, 3H), 3.08 (d, *J* = 13.6 Hz, 1H), 6.59–6.72 (m, 4H), 6.93–7.01 (m, 2H), 7.02–7.09 (m, 1H), 9.25–9.65 (br, 2H); ^{13}C NMR (DMSO-d_6) δ 29.6, 36.5, 42.5, 47.2, 111.5, 114.0, 114.9, 123.7, 124.4, 126.1, 131.2, 132.2, 144.4, 156.4,

158.0; HRMS (ESI) calcd for $C_{17}H_{19}N_2O_2$ $(M + NH_4)^+$ 283.1441, found 283.1443; calcd for $C_{17}H_{14}NO_2$ $(M - H)^-$ 264.1030, found 264.1034; HPLC purity: 99.8% (t_R 15.3 min).

6.1.35.

1-(2-Fluoro-4-hydroxybenzyl)-5-hydroxy-2,3-dihydro-1*H*-indene-1-carbonitrile

(**12b**)

The title compound was prepared from **27b** as described for the synthesis of **7c**, and obtained as a white solid (mp 183–186 °C) in 80% yield. ^{1}H NMR (DMSO-d_6) δ 2.24–2.37 (m, 2H), 2.73–2.92 (m, 3H), 3.12 (d, J = 13.8 Hz, 1H), 6.49–6.59 (m, 2H), 6.60–6.69 (m, 2H), 7.01–7.10 (m, 2H), 9.54 (br s, 1H), 9.85 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 29.6, 35.4, 37.0, 47.0, 102.2, 102.5, 111.36, 111.38, 111.6, 112.6, 112.8, 114.1, 123.3, 124.3, 132.0, 132.7, 132.8, 144.3, 158.06, 158.14, 158.3, 160.1, 162.6; HRMS (ESI) calcd for $C_{17}H_{18}FN_2O_2$ $(M + NH_4)^+$ 301.1347, found 301.1347; calcd for $C_{17}H_{13}FNO_2$ $(M - H)^-$ 282.0936, found 282.0939; HPLC purity: 99.6% (t_R 16.2 min).

6.1.36.

1-(2-Chloro-4-hydroxybenzyl)-5-hydroxy-2,3-dihydro-1*H*-indene-1-carbonitrile

(**12c**)

The title compound was prepared from **27c** as described for the synthesis of **7c**, and obtained as an off-white solid (mp 181–184 °C) in 81% yield. ^{1}H NMR (DMSO-d_6) δ 2.26–2.42 (m, 2H), 2.75–2.90 (m, 2H), 2.99 (d, J = 13.9 Hz, 1H), 3.24 (d, J = 13.9 Hz, 1H), 6.62 (dd, J = 2.2, 8.1 Hz, 1H), 6.66 (d, J = 2.2 Hz, 1H), 6.72 (dd, J = 2.5, 8.3 Hz, 1H), 6.80 (d, J = 2.5 Hz, 1H), 6.95 (d, J = 8.1 Hz, 1H), 7.18 (d, J = 8.3 Hz, 1H), 9.54 (br s, 1H), 9.87 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 29.7, 37.0, 38.5, 47.1, 111.6, 114.1, 114.4, 115.8, 123.4, 123.7, 124.4, 131.9, 132.7, 134.5, 144.3, 157.4, 158.1; HRMS (ESI) calcd for $C_{17}H_{18}ClN_2O_2$ $(M + NH_4)^+$ 317.1051, found 317.1050; calcd for $C_{17}H_{13}ClNO_2$ $(M - H)^-$ 298.0640, found 298.0640; HPLC purity: 99.5% (t_R 17.2 min).

6.1.37.

5-Hydroxy-1-(4-hydroxy-2-methylbenzyl)-2,3-dihydro-1*H*-indene-1-carbonitrile (12d)

The title compound was prepared from **27d** as described for the synthesis of **7c**, and obtained as an off-white foam in 93% yield. ^{1}H NMR (DMSO-d_6) δ 1.82 (s, 3H), 2.31–2.46 (m, 2H), 2.77–2.95 (m, 3H), 3.05 (d, J = 13.8 Hz, 1H), 6.50 (d, J = 2.5 Hz, 1H), 6.52–6.59 (m, 2H), 6.66 (d, J = 2.0 Hz, 1H), 6.72 (d, J = 8.3 Hz, 1H), 7.03 (d, J = 8.3 Hz, 1H), 9.22 (s, 1H), 9.50 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 19.3, 29.6, 37.7, 38.6,

47.2, 111.5, 112.6, 113.8, 116.8, 123.9, 124.60, 124.64, 131.7, 132.1, 138.4, 144.3, 156.2, 158.0; HRMS (ESI) calcd for $C_{18}H_{21}N_2O_2$ $(M + NH_4)^+$ 297.1598, found 297.1590; calcd for $C_{18}H_{16}NO_2$ $(M - H)^-$ 278.1187, found 278.1189; HPLC purity: 99.8% (t_R 16.2 min).

6.1.38.

1-(3-Fluoro-4-hydroxybenzyl)-5-hydroxy-2,3-dihydro-1*H*-indene-1-carbonitrile (**12e**)

The title compound was prepared from **27e** as described for the synthesis of **7c**, and obtained as a white solid (mp 179–181 °C) in 78% yield. ^{1}H NMR (DMSO-d_6) δ 2.19–2.37 (m, 2H), 2.65–2.85 (m, 2H), 2.86 (d, J = 13.4 Hz, 1H), 3.12 (d, J = 13.4 Hz, 1H), 6.61–6.69 (m, 2H), 6.78–6.90 (m, 2H), 6.94 (dd, J = 1.9, 12.4 Hz, 1H), 7.03–7.10 (m, 1H), 9.54 (br s, 1H), 9.77 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 29.6, 36.6, 42.0, 47.1, 111.5, 114.1, 117.31, 117.34, 117.6, 117.8, 123.5, 124.5, 126.32, 126.35, 127.2, 127.3, 132.0, 143.8, 144.0, 144.5, 149.2, 151.6, 158.0; HRMS (ESI) calcd for $C_{17}H_{18}FN_2O_2$ $(M + NH_4)^+$ 301.1347, found 301.1343; calcd for $C_{17}H_{13}FNO_2$ $(M - H)^-$ 282.0936, found 282.0938; HPLC purity: 99.9% (t_R 16.0 min).

6.1.39.

1-(3-Chloro-4-hydroxybenzyl)-5-hydroxy-2,3-dihydro-1*H*-indene-1-carbonitrile (12f)

The title compound was prepared from **27f** as described for the synthesis of **7c**, and obtained as an off-white foam in 92% yield. ^{1}H NMR (DMSO-d_6) δ 2.20–2.36 (m, 2H), 2.65–2.84 (m, 2H), 2.85 (d, J = 13.4 Hz, 1H), 3.12 (d, J = 13.4 Hz, 1H), 6.61–6.68 (m, 2H), 6.88 (d, J = 8.3 Hz, 1H), 6.97 (dd, J = 2.0, 8.3 Hz, 1H), 7.03–7.10 (m, 1H), 7.15 (d, J = 2.0 Hz, 1H), 9.53 (br s, 1H), 10.12 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 29.6, 36.6, 41.8, 47.1, 111.6, 114.1, 116.2, 119.1, 123.5, 124.5, 127.8, 129.8, 131.4, 132.0, 144.5, 152.2, 158.1; HRMS (ESI) calcd for $C_{17}H_{18}ClN_2O_2$ $(M + NH_4)^+$ 317.1051, found 317.1051; calcd for $C_{17}H_{13}ClNO_2$ $(M - H)^-$ 298.0640, found 298.0642; HPLC purity: 97.4% (t_R 16.9 min).

6.1.40.

5-Hydroxy-1-(4-hydroxy-3-methylbenzyl)-2,3-dihydro-1*H*-indene-1-carbonitrile (12g)

The title compound was prepared from **27g** as described for the synthesis of **7c**, and obtained as an off-white foam in 92% yield. ^{1}H NMR (DMSO-d_6) δ 2.07 (s, 3H),

2.18–2.35 (m, 2H), 2.65–2.85 (m, 3H), 3.05 (d, *J* = 13.3 Hz, 1H), 6.61–6.67 (m, 2H), 6.68 (d, *J* = 8.1 Hz, 1H), 6.81 (dd, *J* = 1.9, 8.1 Hz, 1H), 6.89 (d, *J* = 1.9 Hz, 1H), 7.04-7.10 (m, 1H), 9.22 (s, 1H), 9.50 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 16.1, 29.6, 36.6, 42.6, 47.3, 111.5, 114.0, 114.2, 123.3, 123.7, 124.5, 126.0, 128.4, 132.4, 132.5, 144.5, 154.5, 158.0; HRMS (ESI) calcd for $C_{18}H_{21}N_2O_2$ $(M + NH_4)^+$ 297.1598, found 297.1597; calcd for $C_{18}H_{16}NO_2$ $(M - H)^-$ 278.1187, found 278.1184; HPLC purity: 99.2% (t_R 16.7 min).

6.1.41. 2-[5-Methoxy-1-(4-methoxybenzyl)-2,3-dihydro-1*H*-inden-1-yl]acetaldehyde (28)

To a solution of **27a** (733 mg, 2.50 mmol) in toluene (10.0 mL) was added dropwise DIBAL-H (1.03 M in Hexane, 2.67 mL, 2.75 mmol) at −78 °C, and the mixture was stirred at the same temperature for 1 h. After addition of 2 N HCl (10 mL), the resulting mixture was stirred at room temperature for 2 h, poured into water, and then extracted with EtOAc. The extract was washed with brine, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (gradient: 10–25% EtOAc in hexane) to give 5-methoxy-1-(4-methoxybenzyl)-2,3-dihydro-1*H*-indene-1-carbaldehyde (650 mg,

88%) as a pale yellow oil. This aldehyde (650 mg, 2.19 mmol) was dissolved in THF (3.29 mL), and added dropwise to a mixture prepared by an addition of *n*-BuLi (2.66 M in Hex, 1.73 mL, 4.60 mmol) into the suspension of (methoxymethyl)triphenylphosphonium chloride (1.65 g, 4.83 mmol) in THF (11.0 mL) under ice-cooling and stirring for 30 min. The reaction mixture was stirred at room temperature overnight, before being diluted with water, and the mixture was extracted with EtOAc. The extract was washed with brine, dried over anhydrous $MgSO_4$, and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (gradient: 5–15% EtOAc in hexane) to give 5-methoxy-1-(2-methoxyethenyl)-1-(4-methoxybenzyl)-2,3-dihydro-1*H*-indene (544 mg, 77%) as a pale yellow oil. This intermediate (544 mg, 1.68 mmol) was dissolved in THF (11.7 mL). After addition of 2 N HCl (1.7 mL), the mixture was heated with stirring at 75 °C for 2 h, and then allowed to cool to room temperature. The reaction mixture was poured into water, and the resulting mixture was extracted with EtOAc. The extract was washed with water and brine, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (gradient: 5–20% EtOAc in hexane) to give **28** (485 mg, 93%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.99–2.10 (m, 1H), 2.21–2.30 (m, 1H),

2.51–2.62 (m, 1H), 2.66 (dd, *J* = 2.1, 15.4 Hz, 1H), 2.68–2.79 (m, 2H), 2.81 (d, *J* = 13.3 Hz, 1H), 2.86 (d, *J* = 13.3 Hz, 1H), 3.77 (s, 3H), 3.79 (s, 3H), 6.69–6.75 (m, 4H), 6.76–6.81 (m, 2H), 6.87 (d, *J* = 8.3 Hz, 1H), 9.63–9.67 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 30.5, 37.0, 45.7, 49.8, 52.3, 55.3, 55.5, 110.0, 112.4, 113.3, 124.4, 129.8, 131.5, 139.3, 145.3, 158.3, 159.4, 203.5; HRMS (ESI) calcd for $C_{20}H_{23}O_3$ $(M + H)^+$ 311.1642, found 311.1641.

6.1.42. 2-[5-Methoxy-1-(4-methoxybenzyl)-2,3-dihydro-1*H*-inden-1-yl]acetonitrile (**29**)

A mixture of **28** (186 mg, 0.60 mmol) and hydroxylamine hydrochloride (50 mg, 0.72 mmol) in 1-methyl-2-pyrrolidone (2.4 mL) was heated with stirring at 130 °C overnight. The reaction mixture was allowed to cool to room temperature, poured into water, and extracted with EtOAc. The extract was washed with water and brine, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (gradient: 15–30% EtOAc in hexane) to give **29** (160 mg, 87%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.92–2.02 (m, 1H), 2.22–2.31 (m, 1H), 2.48 (d, *J* = 16.6 Hz, 1H), 2.54–2.69 (m, 2H), 2.74–2.85 (m, 1H), 2.89 (d, *J* = 13.6 Hz, 1H), 3.00 (d, *J* = 13.6 Hz, 1H), 3.78 (s, 3H), 3.79 (s, 3H),

6.71–6.80 (m, 4H), 6.87–7.00 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 28.0, 30.1, 37.5, 43.9, 49.7, 55.3, 55.5, 110.2, 112.5, 113.6, 118.8, 124.2, 129.1, 131.4, 137.9, 145.3, 158.6, 159.8; HRMS (ESI) calcd for $C_{20}H_{22}NO_2$ $(M + H)^+$ 308.1645, found 308.1641.

6.1.43. 2-[5-Hydroxy-1-(4-hydroxybenzyl)-2,3-dihydro-1*H*-inden-1-yl]acetonitrile (**13**)

A mixture of **29** (80 mg, 0.26 mmol) and pyridine hydrochloride (800 mg, 6.92 mmol) was heated with stirring at 220 °C for 30 min. The reaction mixture was allowed to cool to room temperature, and partitioned between EtOAc and water. The organic layer was separated, washed with water and brine, and then dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (gradient: 30–50% EtOAc in hexane) to give **13** (55 mg, 76%) as a white solid (mp 210–212 °C). ^{1}H NMR (DMSO-d_6) δ 1.76–1.87 (m, 1H), 2.04–2.15 (m, 1H), 2.24–2.37 (m, 1H), 2.59–2.81 (m, 5H), 6.51 (d, J = 2.0 Hz, 1H), 6.54–6.63 (m, 3H), 6.69–6.75 (m, 2H), 7.01 (d, J = 8.3 Hz, 1H), 9.21 (s, 1H), 9.22 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 27.6, 29.5, 35.6, 44.0, 49.2, 111.1, 113.4, 114.7, 119.5, 123.8, 127.4, 131.0, 136.4, 145.0, 155.8, 157.0; HRMS (ESI) calcd for $C_{18}H_{21}N_2O_2$ $(M + NH_4)^+$ 297.1598, found 297.1599; calcd for $C_{18}H_{16}NO_2$ $(M - H)^-$

278.1187, found 278.1189; HPLC purity: 99.6% (t_R 15.5 min).

6.1.44.

(4*R*)-3-[(1*R*)-5-Methoxy-2,3-dihydro-1*H*-indene-1-carbonyl]-4-phenyl-1,3-oxazolidin-2-one (***R*,*R*-30**) and **(4*R*)-3-[(1*S*)-5-Methoxy-2,3-dihydro-1*H*-indene-1-carbonyl]-4-phenyl-1,3-oxazolidin-2-one** (***R*,*S*-30**)

To a solution of **14** (384 mg, 2.00 mmol) and DMF (0.01 mL) in DCM (6.0 mL) was added oxalyl chloride (381 mg, 3.00 mmol), and the mixture was stirred at room temperature for 1 h, before being concentrated under reduced pressure. The residue was suspended in THF (4.0 mL), and added dropwise to a mixture prepared by an addition of *n*-BuLi (2.66 M in Hex, 1.05 mL, 2.79 mmol) into the solution of (*R*)-4-phenyl-2-oxazolidinone (482 mg, 2.96 mmol) in THF (8.0 mL) at −78 °C and stirring for 15 min. The reaction mixture was stirred at −78 °C for 30 min, and at room temperature for 2 h. After addition of saturated aqueous NH_4Cl solution, the reaction mixture was extracted with EtOAc. The extract was washed with brine, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (gradient: 20–33% EtOAc in

hexane) to give a less polar product (285 mg, 42%) and a more polar product (292 mg, 43%). The less polar product (280 mg) was dissolved in EtOAc (2.8 mL) at 75 °C, and the solution was allowed to cool to room temperature. The solution was stirred at room temperature for 1 h, and the resulting suspension was diluted with hexane (14.0 mL), and stirred at room temperature for 2 h. The precipitate was collected by filtration, washed with 10% EtOAc in hexane, and dried under reduce pressure to give ***R*,*R*-30** (257 mg) as a white crystal (mp 159–161 °C). The more polar product (290 mg) was treated in the same procedure to give ***R*,*S*-30** (259 mg) as a white crystal (mp 136–138 °C). ***R*,*R*-30** ^{1}H NMR ($CDCl_3$) δ 2.08–2.19 (m, 1H), 2.46–2.58 (m, 1H), 2.82–3.03 (m, 2H), 3.77 (s, 3H), 4.33 (dd, *J* = 3.8, 8.8 Hz, 1H), 4.73 (t, *J* = 8.8 Hz, 1H), 5.24 (dd, *J* = 5.1, 8.7 Hz, 1H), 5.43 (dd, *J* = 3.8, 8.8 Hz, 1H), 6.69–6.77 (m, 2H), 7.16 (d, *J* = 8.3 Hz, 1H), 7.28–7.41 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 30.6, 32.1, 48.7, 55.5, 58.1, 70.1, 110.1, 112.7, 125.8, 126.1, 128.9, 129.3, 132.6, 139.3, 146.5, 153.9, 159.7, 174.3; HRMS (ESI) calcd for $C_{20}H_{20}NO_4$ $(M + H)^+$ 338.1387, found 338.1380. ***R*,*S*-30** ^{1}H NMR ($CDCl_3$) δ 2.34–2.47 (m, 2H), 2.82–2.93 (m, 1H), 3.00–3.12 (m, 1H), 3.76 (s, 3H), 4.30 (dd, *J* = 4.1, 8.9 Hz, 1H), 4.74 (t, *J* = 8.9 Hz, 1H), 5.27–5.33 (m, 1H), 5.47 (dd, *J* = 4.1, 8.9 Hz, 1H), 6.67 (dd, *J* = 2.5, 8.4 Hz, 1H), 6.74 (d, *J* = 2.5 Hz, 1H), 7.12 (d, *J* = 8.4 Hz, 1H), 7.20–7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 30.0, 32.2, 48.5, 55.5, 58.0, 70.0,

110.1, 112.7, 125.5, 125.8, 128.8, 129.3, 132.9, 139.0, 146.4, 154.0, 159.7, 174.2; HRMS (ESI) calcd for $C_{20}H_{20}NO_4$ $(M + H)^+$ 338.1387, found 338.1379.

6.1.45. (1*R*)-(5-Methoxy-2,3-dihydro-1*H*-inden-1-yl)(4-methoxyphenyl)methanone (*R*-15a)

To a solution of ***R*,*R*-30** (337 mg, 1.00 mmol) in THF (20.0 mL) was added dropwise a solution prepared by an addition of 30% aqueous hydrogen peroxide solution (0.57 mL) into the solution of LiOH monohydrate (50 mg, 1.20 mmol) in water (4.0 mL) under ice-cooling. After stirring under ice-cooling for 3 h, 2 M aqueous sodium sulfite solution (5.0 mL) was added to the mixture, and the mixture was stirred at room temperature for 30 min. The mixture was poured into 1 N HCl (15 mL), and the resulting mixture was extracted with EtOAc. The extract was washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was dissolved in DCM (8.0 mL), and *N*,*O*-dimethylhydroxylamine hydrochloride (195 mg, 2.00 mmol), HOBt·H_2O (184 mg, 1.20 mmol), and EDCI·HCl (288 mg, 1.50 mmol) were added to the solution. To the mixture was added dropwise Et_3N (152 mg, 1.50 mmol) under ice-cooling, and the mixture was stirred at room temperature overnight. The reaction mixture was poured into water, and the resulting

mixture was extracted with EtOAc. The extract was washed successively with water, saturated aqueous $NaHCO_3$ solution and brine, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (gradient: 20–50% EtOAc in hexane) to give (1*R*)- *N*,5-dimethoxy-*N*-methyl-2,3-dihydro-1*H*-indene-1-carboxamide (206 mg, 88%). This intermediate (205 mg, 0.87 mmol) was dissolved in THF (13.1 mL). To the solution was added dropwise 4-methoxyphenyl magnesium bromide (0.5 M in THF, 4.35 mL, 2.18 mmol) under ice-cooling, and the mixture was stirred at same temperature for 3 h. After addition of saturated aqueous NH_4Cl solution, the mixture was extracted with EtOAc. The extract was washed with water and brine, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (gradient: 10–25% EtOAc in hexane) to give ***R*-15a** (140 mg, 57%) as a white solid (mp 120–122 °C). ^{1}H NMR ($CDCl_3$) δ 2.36–2.56 (m, 2H), 2.92–3.02 (m, 1H), 3.08–3.18 (m, 1H), 3.77 (s, 3H), 3.90 (s, 3H), 4.90–4.97 (m, 1H), 6.65 (dd, *J* = 2.5, 8.4 Hz, 1H), 6.82 (d, *J* = 2.5 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 6.96–7.02 (m, 2H), 8.01–8.08 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 30.1, 32.4, 51.5, 55.5, 55.6, 110.2, 112.5, 114.0, 125.6, 130.1, 131.3, 134.1, 146.4, 159.5, 163.7, 199.3; HRMS (ESI) calcd for $C_{18}H_{19}O_3$ $(M + H)^+$ 283.1329, found 283.1325.

6.1.46. (1*S*)-(5-Methoxy-2,3-dihydro-1*H*-inden-1-yl)(4-methoxyphenyl)methanone (*S*-15a)

The title compound was prepared from ***R*,*S*-30** as described for the synthesis of ***R*-15a**, and obtained as a white solid (mp 119–122 °C) in 44% yield. ^{1}H NMR ($CDCl_3$) δ 2.36–2.56 (m, 2H), 2.92–3.03 (m, 1H), 3.08–3.19 (m, 1H), 3.77 (s, 3H), 3.90 (s, 3H), 4.90–4.97 (m, 1H), 6.65 (dd, *J* = 2.3, 8.4 Hz, 1H), 6.82 (d, *J* = 2.3 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 6.96–7.02 (m, 2H), 8.01–8.08 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 30.1, 32.4, 51.5, 55.5, 55.6, 110.2, 112.5, 114.0, 125.6, 130.1, 131.3, 134.1, 146.4, 159.5, 163.7, 199.3; HRMS (ESI) calcd for $C_{18}H_{19}O_3$ $(M + H)^+$ 283.1329, found 283.1320.

6.1.47. (1*S*)-1-(4-Hydroxybenzyl)-2,3-dihydro-1*H*-inden-5-ol (*S*-7a)

The title compound was prepared from ***R*-15a** as described for the synthesis of **7a**, and obtained as an off-white solid (mp 165–167 °C) in 91% yield. ^{1}H NMR (DMSO-d_6) δ 1.56–1.67 (m, 1H), 1.91–2.02 (m, 1H), 2.44 (dd, *J* = 9.2, 13.4 Hz, 1H), 2.56–2.76 (m, 2H), 2.90 (dd, *J* = 5.7, 13.4 Hz, 1H), 3.13–3.23 (m, 1H), 6.49 (dd, *J* = 2.2, 8.0 Hz, 1H), 6.57 (d, *J* = 2.2 Hz, 1H), 6.63–6.69 (m, 2H), 6.88 (d, *J* = 8.0 Hz, 1H), 6.95–7.02 (m, 2H), 9.06 (br s, 1H), 9.14 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 30.7, 31.6,

40.3, 45.3, 111.1, 112.9, 114.9, 124.1, 129.8, 130.8, 136.9, 144.9, 155.4, 156.2; HRMS (ESI) calcd for $C_{16}H_{17}O_2$ $(M + H)^+$ 241.1223, found 241.1226; calcd for $C_{16}H_{15}O_2$ $(M - H)^-$ 239.1078, found 239.1083; HPLC purity: 98.8% (t_R 17.3 min); Optical purity: 98.3% ee; $[\alpha]_D^{19}$ +3.01 (*c* 1.13, EtOH).

6.1.48. (1*R*)-1-(4-Hydroxybenzyl)-2,3-dihydro-1*H*-inden-5-ol (*R*-7a)

The title compound was prepared from ***S*-15a** as described for the synthesis of **7a**, and obtained as an off-white solid (mp 165–168 °C) in 81% yield. ^{1}H NMR (DMSO-d_6) δ 1.56–1.67 (m, 1H), 1.91–2.02 (m, 1H), 2.44 (dd, *J* = 9.2, 13.4 Hz, 1H), 2.56–2.76 (m, 2H), 2.90 (dd, *J* = 5.5, 13.4 Hz, 1H), 3.13–3.23 (m, 1H), 6.49 (dd, *J* = 2.2, 8.1 Hz, 1H), 6.57 (d, *J* = 2.2 Hz, 1H), 6.63–6.69 (m, 2H), 6.88 (d, *J* = 8.1 Hz, 1H), 6.95–7.02 (m, 2H), 9.05 (s, 1H), 9.14 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 30.7, 31.6, 40.3, 45.3, 111.1, 112.9, 114.9, 124.1, 129.8, 130.8, 136.9, 144.9, 155.4, 156.2; HRMS (ESI) calcd for $C_{16}H_{17}O_2$ $(M + H)^+$ 241.1223, found 241.1223; calcd for $C_{16}H_{15}O_2$ $(M - H)^-$ 239.1078, found 239.1079; HPLC purity: 98.1% (t_R 17.2 min); Optical purity: 98.6% ee; $[\alpha]_D^{19}$ −3.15 (*c* 1.27, EtOH).

6.1.49. 5-Methoxy-1-(4-methoxybenzyl)-2,3-dihydro-1*H*-indene-1-carboxylic acid

(**31**)

To a mixture of **14** (1.13 g, 5.89 mmol) in MeOH (11.8 mL) was added sulfuric acid (0.07 mL), and the mixture was heated with stirring at 70 °C for 4 h. After the reaction mixture was allowed to cool to room temperature, the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (gradient: 10–20% EtOAc in hexane) to give methyl 5-methoxy-2,3-dihydro-1*H*-indene-1-carboxylate (1.11 g, 91%). This ester (619 mg, 3.00 mmol) was dissolved in THF (9.0 mL), and the solution was cooled to −78 °C, added dropwise LDA (1.13 M in THF and hexane, 3.19 mL, 3.60 mmol), and stirred at −78 °C for 15 min. A solution of **26a** (611 mg, 3.90 mmol) in THF (3.0 mL) was added dropwise to the mixture, and the mixture was stirred at the same temperature for 30 min, and then at room temperature for 2 hour. The reaction mixture was poured into aqueous NH_4Cl solution, and the resulting mixture was extracted with EtOAc. The extract was washed with water and brine, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (gradient: 10–25% EtOAc in hexane) to give methyl 5-methoxy-1-(4-methoxybenzyl)-2,3-dihydro-1*H*-indene-1-carboxylate (942 mg, 96%). This intermediate (900 mg) was dissolved in THF (14.0 mL) and MeOH (7.0 mL), and

2 M aqueous LiOH solution (7.0 mL) was added to the solution, and stirred at room temperature for 20 h. The mixture was poured into 1 N HCl (20 mL), and the resulting mixture was extracted with EtOAc. The extract was washed with water and brine, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (gradient: 20–70% EtOAc in hexane) to give **31** (813 mg, 94%) as a white solid (mp 129–131 °C). ^{1}H NMR (DMSO-d_6) δ 1.95–2.05 (m, 1H), 2.30–2.39 (m, 1H), 2.53–2.64 (m, 1H), 2.73–2.84 (m, 2H), 3.29–3.37 (m, 1H), 3.70 (s, 3H), 3.72 (s, 3H), 6.72–6.83 (m, 4H), 6.98–7.06 (m, 2H), 7.29 (d, J = 8.0 Hz, 1H), 12.44 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 30.3, 33.3, 42.7, 54.9, 55.1, 58.7, 109.4, 112.5, 113.3, 125.1, 129.9, 130.8, 136.9, 145.2, 157.8, 159.2, 175.9; HRMS (ESI) calcd for $C_{19}H_{21}O_4$ $(M + H)^+$ 313.1434, found 313.1428; calcd for $C_{19}H_{19}O_4$ $(M - H)^-$ 311.1289, found 311.1295.

6.1.50.

(4*R*)-3-[(1*R*)-5-Methoxy-1-(4-methoxybenzyl)-2,3-dihydro-1*H*-indene-1-carbonyl]-4-phenyl-1,3-oxazolidin-2-one (***R*,*R*-32**)

The title compound was prepared from **31** as described for the synthesis of ***R*,*R*-30**, and obtained as a 1:1 mixture with ***R*,*S*-32**, after purification by flash column

chromatography.

This diastereomixture (584 mg) was dissolved in EtOAc (10 mL) at 70 °C, and the solution was allowed to cool to room temperature. The solution was stirred at room temperature for 30 min, and the resulting suspension was diluted with hexane (30 mL), and stirred at room temperature for 1 h. The precipitate was collected by filtration, washed with 10% EtOAc in hexane, and dried under reduce pressure to give ***R*,*R*-32** (245 mg, 45%) as a white crystal (mp 194–197 °C). ^{1}H NMR ($CDCl_3$) δ 2.01–2.12 (m, 1H), 2.44–2.68 (m, 3H), 3.07 (d, *J* = 13.2 Hz, 1H), 3.51 (d, *J* = 13.2 Hz, 1H), 3.72 (s, 3H), 3.77 (s, 3H), 4.26 (dd, *J* = 3.7, 8.6 Hz, 1H), 4.67 (t, *J* = 8.6 Hz, 1H), 5.48 (dd, *J* = 3.7, 8.6 Hz, 1H), 6.53–6.59 (m, 3H), 6.60–6.66 (m, 2H), 6.71 (dd, *J* = 2.3, 8.5 Hz, 1H), 7.02 (d, *J* = 8.5 Hz, 1H), 7.28–7.45 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 31.2, 33.2, 42.2, 55.2, 55.4, 59.8, 61.9, 70.1, 108.8, 112.4, 113.1, 126.1, 126.8, 128.8, 128.9, 129.4, 131.6, 136.0, 139.5, 146.9, 152.5, 158.2, 159.6, 175.6; HRMS (ESI) calcd for $C_{28}H_{28}NO_5$ $(M + H)^+$ 458.1962, found 458.1959.

6.1.51.

(4*S*)-3-[(1*S*)-5-Methoxy-1-(4-methoxybenzyl)-2,3-dihydro-1*H*-indene-1-carbonyl]-4-phenyl-1,3-oxazolidin-2-one (***S*,*S*-32**)

The title compound was prepared as described for the synthesis of ***R*,*R*-32**, using (*S*)-4-phenyl-2-oxazolidinone instead of (*R*)-4-phenyl-2-oxazolidinone, and obtained as a white crystal (mp 194–197 °C) in 44% yield. ^{1}H NMR ($CDCl_3$) δ 2.01–2.12 (m, 1H), 2.44–2.68 (m, 3H), 3.07 (d, *J* = 13.1 Hz, 1H), 3.51 (d, *J* = 13.1 Hz, 1H), 3.72 (s, 3H), 3.77 (s, 3H), 4.26 (dd, *J* = 3.6, 8.6 Hz, 1H), 4.67 (t, *J* = 8.6 Hz, 1H), 5.48 (dd, *J* = 3.6, 8.6 Hz, 1H), 6.53–6.59 (m, 3H), 6.60–6.66 (m, 2H), 6.71 (dd, *J* = 2.4, 8.5 Hz, 1H), 7.03 (d, *J* = 8.5 Hz, 1H), 7.28–7.45 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 31.2, 33.2, 42.2, 55.2, 55.4, 59.8, 61.9, 70.1, 108.8, 112.4, 113.1, 126.1, 126.8, 128.8, 128.9, 129.4, 131.6, 136.0, 139.5, 146.9, 152.5, 158.2, 159.6, 175.6; HRMS (ESI) calcd for $C_{28}H_{28}NO_5$ $(M + H)^+$ 458.1962, found 458.1960.

6.1.52. (1*R*)-5-Hydroxy-1-(4-hydroxybenzyl)-2,3-dihydro-1*H*-indene-1-carbonitrile (***R*-12a**)

To a solution of ***R*,*R*-32** (197 mg, 0.43 mmol) in THF (8.6 mL) was added dropwise a solution prepared by an addition of 30% aqueous hydrogen peroxide solution (0.20 mL) into the solution of LiOH monohydrate (36 mg, 0.86 mmol) in water (1.7 mL) under ice-cooling. After stirring under ice-cooling for 3 h, 2 M aqueous sodium sulfite solution (2.2 mL) was added to the mixture, and the mixture was stirred

at room temperature for 30 min. The mixture was poured into 1 N HCl (20 mL), and the resulting mixture was extracted with EtOAc. The extract was washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (gradient: 30–60% EtOAc in hexane) to give (1*R*)-5-methoxy-1-(4-methoxybenzyl)-2,3-dihydro-1*H*-indene-1-carboxylic acid (105 mg). This carboxylic acid (105 mg) was dissolved in THF (3.4 mL). To the solution was added 1,1'-carbonyldiimidazole (109 mg, 0.67 mmol), and the mixture was stirred at room temperature for 1 h. After addition of 28% aqueous NH_3 solution (1.7 mL), the mixture was stirred at room temperature for 1 h. The mixture was poured into water, and the resulting mixture was extracted with EtOAc twice. The combined extracts were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on NH silica gel (gradient: 40–85% EtOAc in hexane) to give (1*R*)-5-methoxy-1-(4-methoxybenzyl)-2,3-dihydro-1*H*-indene-1-carboxamide (83 mg). This intermediate (83 mg) was dissolved in DCM (2.7 mL), and Et_3N (161 mg, 1.59 mmol) was added to the solution. Trifluoroacetic anhydride (167 mg, 0.80 mmol) was added dropwise to the solution under ice-cooling, and the mixture was stirred at the

same temperature for 15 min, and at room temperature for 2 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ solution, and the resulting mixture was extracted with EtOAc. The extract was washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (gradient: 10–25% EtOAc in hexane) to give (1*R*)-5-methoxy-1-(4-methoxybenzyl)-2,3-dihydro-1*H*-indene-1-carbonitrile (75 mg, 59% in 3 steps).

The title compound was prepared from this cyanide as described for the synthesis of 7c, and obtained as a white solid (mp 185–187 °C) in 87% yield. ^{1}H NMR (DMSO-d_6) δ 2.18–2.35 (m, 2H), 2.65–2.87 (m, 3H), 3.08 (d, J = 13.6 Hz, 1H), 6.59–6.72 (m, 4H), 6.93–7.01 (m, 2H), 7.02–7.09 (m, 1H), 9.34 (br s, 1H), 9.51 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 29.6, 36.5, 42.5, 47.2, 111.5, 114.0, 114.9, 123.7, 124.4, 126.1, 131.2, 132.2, 144.4, 156.4, 158.0; HRMS (ESI) calcd for $C_{17}H_{19}N_2O_2$ $(M + NH_4)^+$ 283.1441, found 283.1439; calcd for $C_{17}H_{14}NO_2$ $(M - H)^-$ 264.1030, found 264.1029; HPLC purity: 99.7% (t_R 15.3 min); Optical purity: > 99% ee; $[\alpha]_D^{19}$ +63.7 (*c* 1.23, EtOH).

6.1.53. (1*S*)-5-Hydroxy-1-(4-hydroxybenzyl)-2,3-dihydro-1*H*-indene-1-carbonitrile

(***S*-12a**)

The title compound was prepared from ***S*,*S*-32** as described for the synthesis of ***R*-12a**, and obtained as a white solid (mp 185–188 °C) in 58% yield. ^{1}H NMR (DMSO-d_6) δ 2.18–2.35 (m, 2H), 2.65–2.87 (m, 3H), 3.08 (d, J = 13.6 Hz, 1H), 6.60–6.71 (m, 4H), 6.94–7.01 (m, 2H), 7.03–7.09 (m, 1H), 9.33 (s, 1H), 9.50 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 29.6, 36.5, 42.5, 47.2, 111.5, 114.0, 114.9, 123.7, 124.4, 126.1, 131.2, 132.2, 144.5, 156.5, 158.0; HRMS (ESI) calcd for $C_{17}H_{19}N_2O_2$ $(M + NH_4)^+$ 283.1441, found 283.1438; calcd for $C_{17}H_{14}NO_2$ $(M - H)^-$ 264.1030, found 264.1033; HPLC purity: 99.6% (t_R 15.3 min); Optical purity: > 99% ee; $[\alpha]_D^{19}$ −63.5 (*c* 1.24, EtOH).

6.2. Biological methods

The expression vectors for human ERα and human ERβ were constructed by inserting the cDNA of ERs from plasmid (OriGene, Rockville, MD) into pcDNA3.1 vectors. The estrogen responsive reporter plasmid, pGL4.27-$(ERE)_3$-Luc, was constructed by inserting the three repeats of estrogen responsive element (ERE) into the XhoI/HindIII sites of pGL4.27 vector (Promega, Madison, WI). The plasmid phRL-TK (Promega), which contains the Renilla luciferase gene, was used as an internal control

for transfection efficiency.

6.2.1. Estrogen receptor binding assays

The binding affinities for ERs were determined by a fluorescence polarization displacement assay using PolarScreen ER Competitor Assay Green kits (Thermo Fisher Scientific) according to the manufacturer's instructions, and are expressed as relative binding affinity (RBA) values compared to the affinity of **E2** (=100).

6.2.2. Cell based ERα and ERβ assays

HEK293T cells were maintained in DMEM (Thermo Fisher Scientific, Waltham, MA) supplemented with 10% fetal bovine serum. The day before transfection, the medium was replaced with phenol red-free DMEM (Thermo Fisher Scientific) supplemented with 10% charcoal-stripped FBS and 2 mM glutamine. Transfection assays were performed in 384-well plates using 10 µL of serum-free Opti-MEM medium (Thermo Fisher Scientific) containing 0.08 µL of Lipofectamine2000 (Thermo Fisher Scientific), 36 ng of pGL4.27-$(ERE)_3$-Luc, 0.8 ng of phRL-TK and 4 ng of expression vector containing ERα or ERβ per well. Compounds were added to the cells 8 h after transfection and were cultured for another 16 h. Luciferase activity was measured by a Dual-Glo Luciferase assay system (Promega) according to the

manufacturer's instructions. The transcriptional activity of each compound was normalized by the hypothetical maximal response of **E2** (=100) calculated from GraphPad Prism with sigmoidal dose response algorithm.

6.3. Molecular modeling

The coordinates of ERβ for the docking study of ***R*-12a** were prepared from the X-ray structure of ERβ complexed with ERB-041 (the A-chain of Protein Data Bank entry 1X7B).[34] For the protein, hydrogen atoms were generated using the Accelrys Discovery Studio 4.5 with default settings (Glu and Asp are negatively charged, Arg and Lys are positively charged, and the other amino acids are neutral). Exceptionally, the N-H hydrogen in the imidazole ring of His475 was moved from the δ-position to the ε-position in consideration of a hydrogen bond with the backbone carbonyl group of Glu371.

Three-dimensional conformations of ***R*-12a** were generated by OMEGA[39] under conditions that the phenol and the indane rings were rotated from 0 to 350 degrees at 10 degree increments.

The docking was performed using FRED[40] with default setting except for selecting the "high resolution" option. The docking pose observed at the highest score

was selected.

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26. In ***R***,***R*-30**, ***R***,***S*-30**, ***R***,***R*-32**, and ***S***,***S*-32**, the absolute configurations of indane-1-position were determined by X-ray crystallography. The crystal structures of ***R***,***R*-30**, ***R***,***S*-30**, ***R***,***R*-32**, and ***S***,***S*-32** have been deposited at the Cambridge Crystallographic Data Centre and the CCDC deposition number are 1480233, 1480245, 1480249 and 1480253, respectively.

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Legends

Figure 1. Estradiol and ERβ ligands.

Figure 2. Compounds of interest.

Figure 3. The most likely binding conformation of ***R*-12a** (stick, colored by element) docked into the ligand binding cavity of ERβ (red line ribbons) complexed with

ERB-041 **3a** (green stick). Only key residues are displayed for simplicity (ball and stick, colored by element). Potential hydrogen bonds to key residues are shown as as blue lines.

Table 1. Binding affinities and transcriptional activities for ERs and ERβ selectivities of 1-benzylindane derivative **7a** and related compounds. [a]Relative binding affinity (RBA) values were calculated by IC_{50}[**E2**]/IC_{50}[test compound] × 100 (RBA of **E2** = 100), shown as mean ± SD of three or four independent experiments, performed in duplicate. [b]β/α values = ERβ-RBA/ERα-RBA (ERβ selectivity of binding affinity). [c]Log *P* values were calculated using Marvin 6. 2. 0 (ChemAxon). [d]EC_{50} values are shown as Mean ± SD of three independent experiments, performed in duplicate. [e]Rel.β/α values = {ERβ-EC_{50}[**E2**]/ERβ-EC_{50}[compound]}/{ERα-EC_{50}[**E2**]/ERα-EC_{50}[compound]} (ERβ selectivity of agonistic activity). [f]The value is the reporter activation at 10 μM, normalized by the maximum response of **E2**, which is set as 100%.

Table 2. Binding affinities and transcriptional activities for ERs and ERβ selectivities of 1-benzylindane derivatives with substitutions on linker carbons and pendant phenyl group. [a]Relative binding affinity (RBA) values were calculated by IC_{50}[**E2**]/IC_{50}[test compound] × 100 (RBA of **E2** = 100), shown as mean ± SD of three or four independent experiments, performed in duplicate. [b]β/α values = ERβ-RBA/ERα-RBA

(ERβ selectivity of binding affinity). [c]Log *P* values were calculated using Marvin 6. 2. 0 (ChemAxon). [d]EC_{50} values are shown as Mean ± SD of three independent experiments, performed in duplicate. [e]Rel.β/α values = {ERβ-EC_{50}[**E2**]/ERβ-EC_{50}[compound]}/{ERα-EC_{50}[**E2**]/ERα-EC_{50}[compound]} (ERβ selectivity of agonistic activity). [f]The value is the reporter activation at 3 μM, normalized by the maximum response of **E2**, which is set as 100%.

Table 3. Binding affinities and transcriptional activities for ERs and ERβ selectivities of the enantiomers of **7a** and **12a**. [a]Relative binding affinity (RBA) values were calculated by IC_{50}[**E2**]/IC_{50}[test compound] × 100 (RBA of **E2** = 100), shown as mean ± SD of three or four independent experiments, performed in duplicate. [b]β/α values = ERβ-RBA/ERα-RBA (ERβ selectivity of binding affinity). [c]EC_{50} values are shown as Mean ± SD of three independent experiments, performed in duplicate. [d]Rel.β/α values = {ERβ-EC_{50}[**E2**]/ERβ-EC_{50}[compound]}/{ERα-EC_{50}[**E2**]/ERα-EC_{50}[compound]} (ERβ selectivity of agonistic activity).

Scheme 1. Reagents and conditions: (a) MeONHMe·HCl, EDCI·HCl, HOBt·H_2O, Et_3N, CH_2Cl_2, 0 °C to rt; (b) 4-(or 3-)MeO–PhMgBr, THF, 0 °C to rt; (c) Et_3SiH, TFA, 0 °C to rt; (d) BBr_3, CH_2Cl_2, −78 °C to rt.

Scheme 2. Reagents and conditions: (a) 4-MeO–BnMgCl, THF, Toluene, 0 °C to rt; (b)

Pd–C, H_2, MeOH, THF, rt; (c) BBr_3, CH_2Cl_2, −78 °C to rt.

Scheme 3. Reagents and conditions: (a) $EtP^+Ph_3Br^-$, *n*-BuLi, THF, 0 °C to rt; (b) Pd–C, H_2, MeOH, THF, rt; (c) BBr_3, CH_2Cl_2, −78 °C to rt.

Scheme 4. Reagents and conditions: (a) NaH, R^1-I, DMF, 0 °C to rt; (b) DIBAL-H, Toluene, −78 °C, then 2 M HCl aq., rt; (c) 4-Br-anisole, *n*-BuLi, THF, −78 °C to rt; (d) Pd–C, H_2, MeOH, THF, rt; (e) BBr_3, CH_2Cl_2, −78 °C to rt.

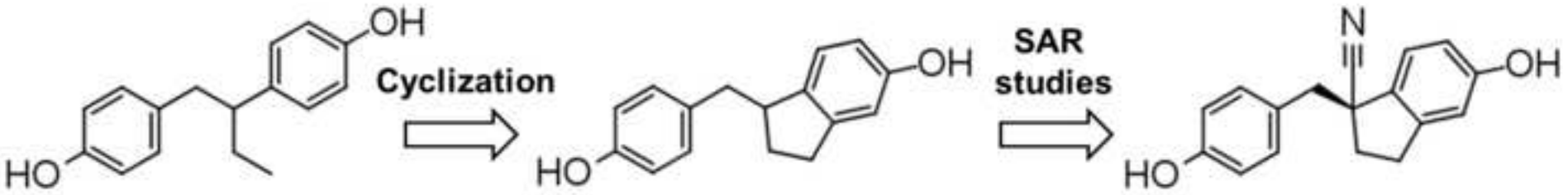
Scheme 5. Reagents and conditions: (a) **26a**–**g**, LDA, THF, −78 °C to rt; (b) BBr_3, CH_2Cl_2, −78 °C to rt.

Scheme 6. Reagents and conditions: (a) DIBAL-H, Toluene, −78 °C, then 2 M HCl aq., rt; (b) $MeOCH_2P^+Ph_3Cl^-$, *n*-BuLi, THF, 0 °C to rt; (c) HCl, THF, 75 °C; (d) $HO–NH_2$·HCl, NMP, 130 °C; (e) Pyridine·HCl, 220 °C.

Scheme 7. Reagents and conditions: (a) (i) $(COCl)_2$, CH_2Cl_2, rt; (ii) (*R*)-4-Ph-oxazolidin-2-one, *n*-BuLi, THF, −78 °C to rt; (b) $LiOH·H_2O$, H_2O_2, THF, H_2O, 0 °C; (c) MeONHMe·HCl, EDCI·HCl, $HOBt·H_2O$, Et_3N, CH_2Cl_2, 0 °C to rt; (d) 4-MeO–PhMgBr, THF, 0 °C; (e) Et_3SiH, TFA, 0 °C to rt; (f) BBr_3, CH_2Cl_2, −78 °C to rt.

Scheme 8. Reagents and conditions: (a) H_2SO_4, MeOH, 70 °C; (b) 4-MeO–BnCl, LDA, THF, −78 °C to rt; (c) $LiOH·H_2O$, THF, MeOH, H_2O, rt; (d) (i) $(COCl)_2$, CH_2Cl_2, rt; (ii) (*R*) (or (*S*))-4-Ph-oxazolin-2-one, *n*-BuLi, THF, −78 °C to rt; (iii) recrystallization; (e)

$LiOH·H_2O$, H_2O_2, THF, H_2O, 0 °C; (f) CDI, THF, rt, then NH_3 aq., rt; (g) TFAA, Et_3N, CH_2Cl_2, 0 °C to rt; (h) BBr_3, CH_2Cl_2, −78 °C to rt.



Isobutestrol 5b

Agonistic activity (EC_{50})

ERα 185 ± 17 nM

ERβ 0.23 ± 0.01 nM

7a

Agonistic activity (EC_{50})

ERα 1,170 ± 265 nM

ERβ 1.14 ± 0.21 nM

***R*-12a**

Agonistic activity (EC_{50})

ERα **2,410** ± 56 nM

ERβ **0.78** ± 0.12 nM