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Chemical studies on the chiral indanone derivatives as the inhibitor of *Renilla* luciferase

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Abstract—The bioluminescence reaction of coelenterazine involves an oxidative process. To investigate the reaction mechanism, we synthesized three mechanism-based inhibitors with an indanone core structure. The inhibitors exhibited the competitive inhibition of the *Renilla* luciferase reaction. The (−)-4-benzyl-2-(4-hydroxybenzyl)-2-hydroxymethyl-6-(4-hydroxyphenyl)-indan-1-one showed the significant enantio-selectivity of the inhibition and its absolute configuration was assigned as the *R*-configuration. These inhibitors could be useful probes to study the catalytic environment in the coelenterazine–luciferase reaction.

1. Introduction[1]

Coelenterazine (**1a**) is well known as a substrate (luciferin) in various bioluminescence reactions of marine organisms, such as jellyfishes,[2] sea pansies[3] and deep-sea shrimps.[4] The bio- and chemiluminescence reaction of coelenterazine (**1a**) is an oxidation process that could involve several intermediates (**2a**,**b**), and then results in light emission (Fig. 1). The efficiency of bioluminescence of coelenterazine catalyzed by luciferase is higher than that of chemiluminescence in polar aprotic solvent. To investigate the intermediates of chemiluminescence, the C-2 peroxide of coelenterazine analog was synthesized by the sensitized photooxidation at −95°C.[5] The synthesis of a ^{13}C-labelled coelenterazine analog was also reported[6] and its photooxidation products have been analyzed by the ^{13}C NMR spectroscopy, which suggest that the C-2 peroxide and dioxetanone are present at low temperature. The model studies

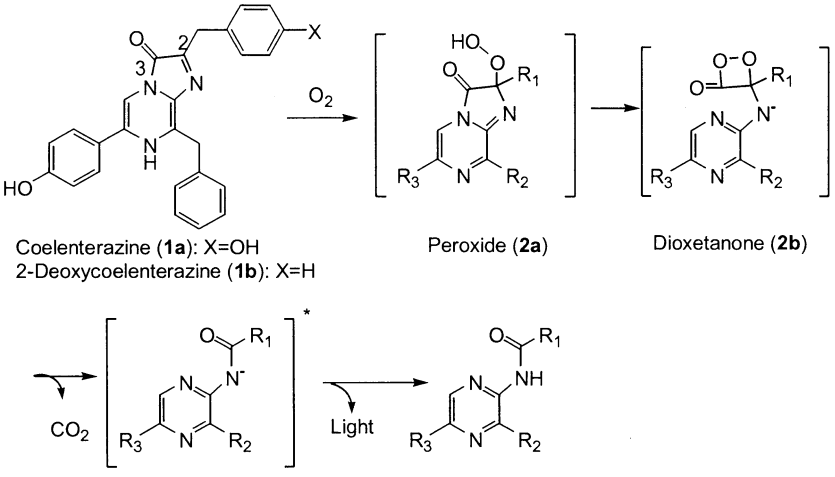

Figure 1. The luminescence mechanism of coelenterazine (**1a**) and possible intermediates (**2a**-**b**).

Keywords: bioluminescence; coelenterazine; peroxide; inhibitor; transition-state.

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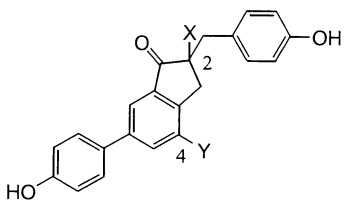


3a : X=H, Y=Benzyl
3b : X=CH_2OH, Y=Benzyl
3c : X=CH_2OH, Y=H

Figure 2. Structure of three mechanism-based inhibitors.

on the chemiluminescence of coelenterazine analogs have suggested that the formation of the C-2 peroxide could be the rate-determining step in the luminescence reaction.[7] The $^{18}O_2$ labeling studies of the intermediates in the bioluminescence reaction with the shrimp luciferase has been reported.[4] Recently, the structure of the C-2 peroxide of coelenterazine with *S*-configuration in aequorin, which is a stable complex in the absence of Ca^{2+}, has been determined by the X-ray crystal structure analysis.[8] This result implied that the catalytic site of luciferase could be chiral and one enantiomer of the peroxide intermediate can fit it properly. However, no investigation of the chiral environment of luciferase has been reported.

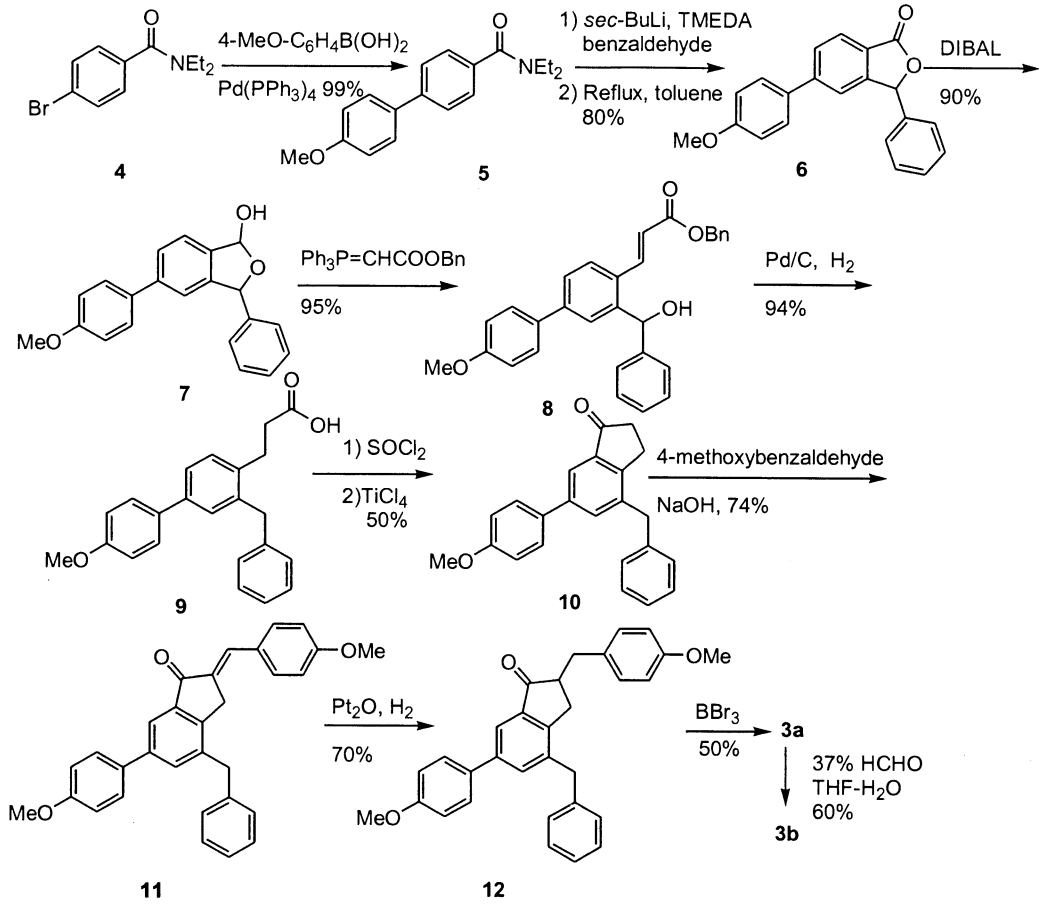
Renilla luciferase was isolated from sea pansy, *Renilla reniformis*, and it catalyzes the oxidation of coelenterazine to emit blue light.[3] The gene encoding *Renilla* luciferase has been cloned and expressed in bacterial cells.[9] A highly purified recombinant *Renilla* luciferase was obtained by the Ni-chelate affinity chromatography.[9] The quantum yield in the luminescence reaction of recombinant *Renilla* luciferase with coelenterazine is 0.10–0.11.[9] The substrate specificity and inhibitory studies on *Renilla* luciferase were reported using several coelenterazine analogs.[3,9]

In this study we designed and synthesized three mechanism-based inhibitors of coelenterazine (**3a**–**c**), having an indanone core structure to overcome the unstable properties of intermediates (Fig. 2). Separation of the enantiomers by a chiral column, determination of their configuration and examination of the inhibition of the recombinant *Renilla* luciferase reaction are also described.

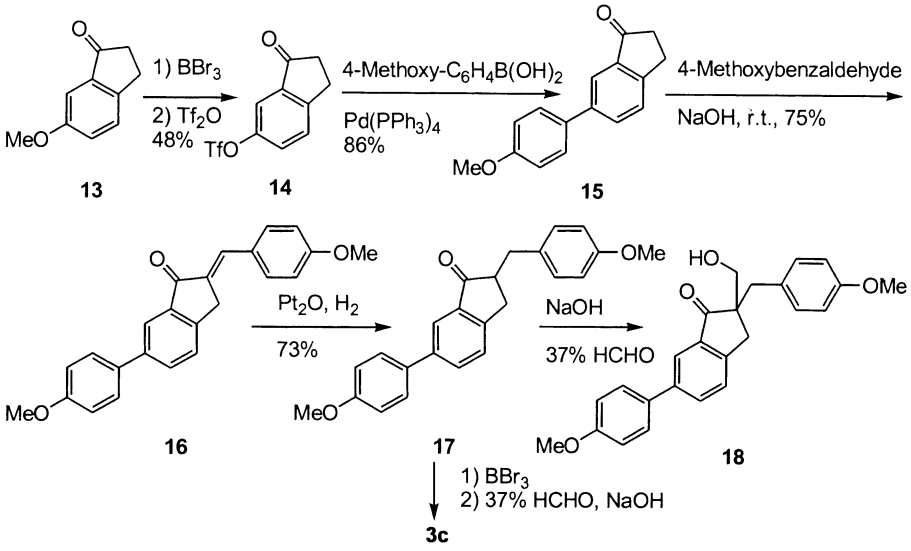
2. Results and discussions

2.1. Preparation of the chiral mechanism-based inhibitors

The synthesis of the inhibitors (**3a**,**b**) was shown in Scheme 1. Under the Suzuki-coupling conditions, the starting material 3-bromobenzamide (**4**) was treated with a boronic reagent to give the biphenyl (**5**) in good yield.[10] A benzyl group was introduced to **5** by the *ortho*-metalation with benzaldehyde and then the product was converted to the lactone (**6**) in 80% overall yield.[11] Reduction of **6** with



Scheme 1. Synthesis of the inhibitors **3a** and **3b**.



Scheme 2. Synthesis of the inhibitor **3c**.

DIBAL provided the hemiacetal (**7**). After the Wittig reaction, catalytic hydrogenation and hydrogenolysis of the product **8** were accomplished in one step to give the acid (**9**) in 94% yield. Acid halide formation of **9** was followed by the intramolecular Friedel–Crafts acylation to give the indanone structure (**10**). A *p*-hydroxybenzyl moiety was introduced by the aldol condensation with *p*-methoxybenzaldehyde to form the *E-exo* olefin (**11**). Hydrogenation of **11** was performed with Pt_2O to give **12**. Deprotection of methyl ether with BBr_3 afforded **3a**, which has a chiral center at C-2 position. The second Aldol condensation of **3a** was performed with the formaldehyde solution to give **3b**. The enantiomers of **3a** and **3b** were separated on a chiral column.

To study the effect of the substituent at the C-4 position of inhibitor on the luminescence reaction, we synthesized the debenzyl analog **3c**. The synthesis of **3c** was accomplished in **7** steps from a commercially available indanone compound (**13**). The synthetic route was shown in Scheme 2. The Suzuki-coupling reaction of the aryl triflate (**14**) with a boronic acid gave **15** in 86% yield. Condensation of **15** with *p*-methoxybenzaldehyde in a basic condition provided **16**. Hydrogenation using Pt_2O followed by the Aldol reaction gave **17**. The Aldol condensation of **17** with the formaldehyde solution gave **18**. Unfortunately, the deprotection of the methyl ether of **18** using BBr_3 led to the retro-Aldol reaction. After the deprotection of **17**, the Aldol condensation afforded (±)-**3c** in 35% overall yield. Resolution of (±)-**3c** was carried out by the same chiral column to give (+)- and (−)-**3c**.

2.2. Assignment of the absolute configurations of inhibitors

The absolute configuration of each enantiomers was determined by the circular dichroic (CD) methods. The conjugated ketone exhibits CD cotton effect in the range of 320–370 nm, which is due to $n\rightarrow\pi^*$ transition. Snatzke has introduced the sector rule to indanone derivatives.[12] In the case of the chiral indanone derivatives with a substituent at C-2 position, the substituent prefers the pseudoequatorial orientation to the pseudoaxial orientation. The 2*S*-configuration exhibits the negative cotton effect, which is explained

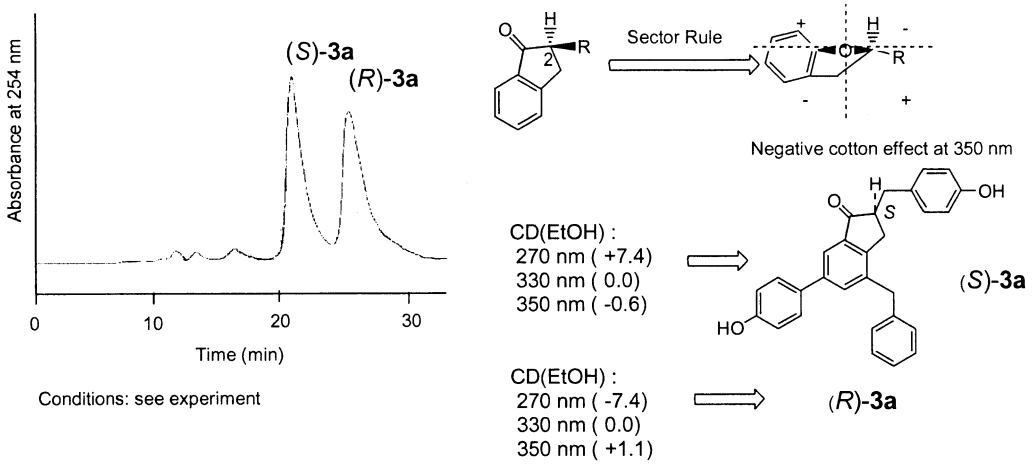
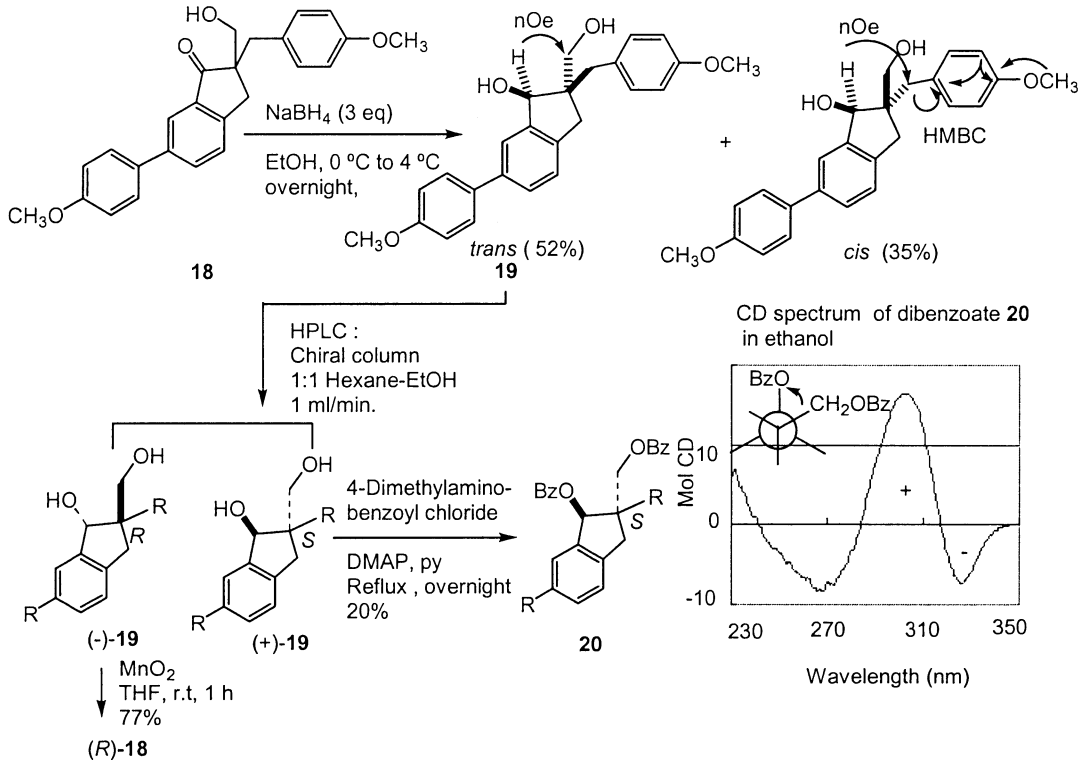


Figure 3. Separation and assignment of the absolute configurations of (+)- and (−)-**3a**.



Scheme 3. Preparation of (*R*)-**18**.

by the octant type projection (Fig. 3).[12] The enantiomer of **3a** showing a negative cotton effect at 350 nm in the CD spectra was determined as the *S*-configuration.

To assign the absolute configurations of **3b** and **3c**, we compared the CD spectra with (*R*)-**18**, which was prepared from its racemic form (Scheme 3). Treatment of (±)-**18** with $NaBH_4$ gave the major diol **19** and the corresponding diastereomer. The *trans* conformation of **19** was characterized by the nOe and HMBC experiments. The both enantiomers (+)- and (−)-**19** were separated by HPLC on the chiral column, and (+)-**19** was treated with 4-dimethylaminobenzoyl chloride to give the dibenzoate derivative **20**. The CD spectrum exhibited negative first and positive second cotton effects, implying that the chiral center at the C-2 position of **20** and (+)-**19** could be determined as the *S*-configuration by the CD dibenzoate chirality rule.[13] On the other hand (−)-**19** was oxidized by using MnO_2 to give (*R*)-**18**. The enantiomers (−)-**3b** and (−)-**3c** having a long retention time on the chiral HPLC exhibited the CD spectra matching (*R*)-**18**; therefore, these enantiomers could be determined as the *R*-configuration (Fig. 4).

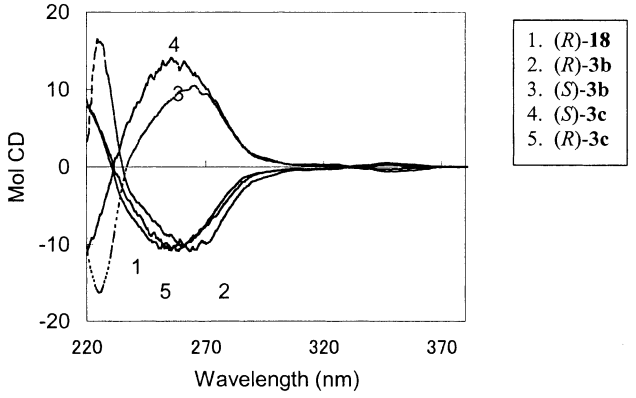


Figure 4. CD spectra of the enantiomers of **3b** and **3c** in comparison with (*R*)-**18**.

The cotton effect of the indanone derivatives with a hydroxymethyl substituent at the C-2 position affected by the solvent polarity has been discussed.[14] The cotton effect of these indanone derivatives in ethanol gives opposite sign to that of chloroform as a solvent. This observation suggests ethanol interrupted the hydrogen bonding between ketone and hydroxymethyl moiety. We thought that the pseudo-equatorial conformation of the benzyl group of **3b** and **3c** in ethanol like the conformation of **3a** could be predominant due to its bulkiness. Thus, these enantiomers of (−)-**3b** and (−)-**3c** could be also determined as the *R*-configuration according to the sector rule of indanone derivatives. Interestingly, all inhibitors having *S*-configuration exhibited a short retention time on the same chiral column.

2.3. Inhibition of the luminescence with *Renilla* luciferase

Renilla luciferase catalyzes the luminescence reaction of coelenterazine (**1a**) or 2-deoxy-coelenterazeine (**1b**) efficiently.[9] According to the previous report for the inhibitory study on *Renilla* luciferase,[3] we chose 2-deoxy-coelenterazine (**1b**) as the substrate. Measurement of the luminescence activity was started by adding a substrate to a mixture of the inhibitor and luciferase. The K_i values were determined from the Lineweaver–Burk plots. The inhibitors **3a** and **3b** showed very strong competitive inhibition. Interestingly, (*R*)-**3b** (K_i=9.3×10^{-9} M) showed much

Table 1. Inhibition of the recombinant *Renilla* luciferase

Compound	K_I/M
(*S*)-**3a**	4.0×10^{-8}
(*S*)-**3b**	2.1×10^{-7}
(*S*)-**3c**	1.2×10^{-7}
(*R*)-**3a**	5.0×10^{-8}
(*R*)-**3b**	9.3×10^{-9}
(*R*)-**3c**	0.9×10^{-7}

stronger inhibitory effect than its enantiomer (*S*)-**3b** (K_i=2.1×10^{-7} M). These results suggested that the recognition of the peroxide intermediates could be enantioselective in the catalytic site of *Renilla* luciferase. On the other hand, (*R*)-and (*S*)-**3a** showed almost same K_i values in the range of 10^{-8} M. This inhibitory result of **3a** resembled the finding in the acetylcholine esterase inhibition.[15] The K_i values for (*S*)- and (*R*)-**3c** were 1.2×10^{-7} and 0.9×10^{-7} M, respectively, which is implying no enantioselectivity of inhibition between the enantiomers of **3c**. In our previous work, the substituent at the C-8 position of coelenterazine corresponding to the C-4 position of indanone could influence the reaction rate and total light with *Renilla* luciferase.[16] These results suggested that the benzyl group at the C-4 of the inhibitor should be necessary to bind on the chiral catalytic site. The moderate inhibitory effect of **3c** suggested that it could be used to develop an affinity column for luciferase. The K_i values of all chiral inhibitors were shown in Table 1. The result of the inhibitor (*R*)-**3b** showed the strongest inhibition, which was the opposite enantioselectivity to the observation from aequorin.[9]

3. Conclusion

In conclusion, we prepared three mechanism-based inhibitors in enantiomerically pure form. The result of inhibition of recombinant *Renilla* luciferase indicated that the stable inhibitor (*R*)-**3b** gave the strongest inhibition with a high enantioselectivity, suggesting that this inhibitor could reflect the chiral environment in the catalytic site of luciferase. It is remarkable that these compounds could be usable as a probe to study on the bioluminescence mechanism of coelenterazine including the structural analysis for the inhibitor–luciferase complex.

4. Experimental

4.1. General

All melting points were recorded on a Yanaco MP-J3 melting point apparatus and were not corrected. UV spectra were taken on a JASCO V-530 spectrometer. Infrared spectra were determined with a JASCO FT/IR-8300 spectrophotometer and were reported in wave number (cm^{-1}). Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Varian Gemini-2000 (300 MHz) or a Brucker ARX-400 (400 MHz) spectrometer. Chemical shifts (δ) were given in parts per million relative to tetramethylsilane (δ 0.00) or CD_3OD (δ 3.30) as an internal standard and coupling constants (J) in Hz. ^{13}C NMR were recorded on a Brucker ARX-400 (100 MHz). Chemical shifts (δ) were given in parts per million relative to $CDCl_3$ (δ 77.0) or CD_3OD (δ 49.0) as an internal standard. Low-resolution mass spectra were recorded on a JEOL JMS-D 100 (EI), a JEOL DX-705L (FAB) or a JEOL Mstation spectrometer. High-resolution mass spectra (HRMS) were recorded on JEOL DX-705L and JEOL Mstation spectrometers. Elemental analyses were tested in the Analytical Laboratory at the school of Bioagricultural Sciences, Nagoya University. Reactions were monitored by thin-layer chromatography (TLC) on 0.25 mm silica gel coated glass plates 60F-254 (Merck, Art 5715) and visualized using UV light and 7% ethanolic phosphomolybdic acid or 2.5% *p*-anisaldehyde solution as developing reagents by heating. Preparative thin-layer chromatography separations were carried out on 0.5 mm silica gel plate 60F-254 (Merck, Art 5774). Silica gel for chromatography was obtained from Cica–Merck (Silica Gel 60, particle size 0.063–0.22 mm A STM). Optical rotations were measured on a JASCO DIP-370 digital polarimeter. Circular dichroism (CD) spectra were measured on a JASCO J-720WN. Anhydrous solvent of ethyl ether, tetrahydrofuran and dichloromethane were purchased from Kanto Chemical. *N*,*N*,*N*,*N*-tetramethylethylene-diamine was purchased from Aldrich. All other commercially available reagents were used without purification. HPLC was carried out using a JASCO PU-880 pump system equipped with a JASCO UV-875 UV/Vis detector. The peak intensity was measured with a photomultiplier tube (Hamamatsu photonics, R105UH) and amplified output of the tube was introduced to an integrator (Atto, Digimini recorder AC 5150). The peak intensities of bioluminescence were measured at final substrate concentration of 1×10^{-7}, 2×10^{-8}, 3.3×10^{-8} M in presence of the recombinant *Renilla* luciferase (500 ng ml^{-1}) in 25 mM Tris–HCl buffer pH 7.5 containing 0.1 M NaCl at 23°C with or without inhibitor (1×10^{-7} M). The inhibitory data of Lineweaver–Burk plots was obtained from Eq. (1) and was summarized in Table 1

$$v = \frac{V_{max}[S]}{K_m(1 + [I]/K_i) + [S]} \quad (1)$$

4.1.1. *N*,*N*-diethyl-4′-Methoxybiphenyl-4-carboxamide (5). 4-Bromo-*N*,*N*-diethyl-benzamide (**4**)[17] (4.0 g, 0.015 mol) was treated with 4-methoxyphenyl-boronic acid (2.83 g, 0.018 mol), 2 M aqueous sodium carbonate solution (9.0 ml, 0.018 mol), tetrakis(triphenylphosphine)palladium(0) (880 mg, 0.75 mmol) in a mixture of benzene (80 ml) and methanol (40 ml) at 80°C for 17 h. The solution was dried over Na_2SO_4 and evaporated. The residue was purified by silica gel column chromatography (CH_2Cl_2, then 1:1 EtOAc–hexane) to give 4.07 g of yellow needles (99%). **5**: mp 96–98°C; ^{1}H NMR (300 MHz, CD_3OD) δ 1.15–1.26 (6H, br), 3.34–3.36 (2H, br), 3.55–3.57 (2H, br), 3.83 (3H, s), 7.01 (2H, d, J=8.5 Hz), 7.42 (2H, d, J=8.5 Hz), 7.59 (2H, d, J=8.5 Hz), and 7.67 (2H, d, J=8.5 Hz); HRMS (EI) Calcd for $C_{15}H_{21}O_2N$ m/z 283.1572, found m/z 283.1546; IR (Nujol) ν_{max} 2925, 2856, 1626, 1604, 1580, 1530, 1500, 1462, 1378, 1310, 1294, 1258, 1200, 1184, 1096, 1064, 1040, 1016, 856, 830, 770, 722 and 660 cm^{-1}.

4.1.2. 5-(4-Methoxyphenyl)-3-phenyl-3*H*-isobenzofuran-

1-one (6) To a solution of TMEDA (1.32 ml, 8.4 mmol) in dry THF (40 ml) was added dropwise *sec*-BuLi (8.1 ml, 8.4 mmol) at −78°C. After several minutes, a solution of **5** (1.01 g, 3.5 mmol) in dry THF (40 ml) was added dropwise over 30 min period. After another 20 min, a solution of benzaldehyde (877 ml, 8.4 mmol) in dry THF (2 ml) was added and the mixture was stirred at −78°C for 20 min. After saturated aqueous ammonium chloride (10 ml) was added, the bath was removed and the solution was allowed to warm up to ambient temperature. THF was removed in vacuo, the aqueous residue was extracted with EtOAc, and the extract was dried over $MgSO_4$. The solvent was removed in vacuo and the residual yellow liquid (1.2 g) was purified by silica gel column chromatography (CH_2Cl_2, then 1:1 hexane–EtOAc) to yield a yellow solid (1.0 g). The product was heated in toluene at reflux for 12 h. Solvent removal in vacuo left a slightly yellowish solid. Recrystallization from Et_2O–hexane gave 900 mg of **6** as a colorless solid (80%). **6**: mp 131–132°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.85 (3H, s), 6.41 (1H, s), 6.96 (2H, d, J=8.7 Hz), 7.50 (2H, d, J=8.7 Hz), 7.72 (1H, d, J=8.7 Hz), 7.96 (1H, d, J=8.7 Hz), 7.43 (1H, s) and 7.31–7.39 (5H, m); HRMS (EI) Calcd for $C_{21}H_{12}O_3$ *m/z* 316.1100, found *m/z* 316.1096; IR (Nujol) ν_{max} 2942, 2852, 1750, 1600, 1522, 1464, 1378, 1312, 1182, 1068, 996, 822, 762 and 722 cm^{-1}.

4.1.3. 5-(4-Methoxyphenyl)-3-phenyl-1,3-dihydroisobenzofuran-1-ol (7). Under nitrogen atmosphere, to a solution of **6** (730 mg, 2.31 mmol) in 10 ml of dry CH_2Cl_2 at −78°C was added DIBAL (2.6 ml of 1 M hexane solution 2.6 mmol) over 30 min. Methanol (10 ml) was added to the reaction mixture, which was then allowed to warm up to ambient temperature. The solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography using CH_2Cl_2 as an eluent to give 654 mg of a white amorphous solid (90%). **7**: mp 83–85°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.02 (0.5H, d, J=7.8 Hz), 3.18 (0.5H, d, J=7.8 Hz), 3.82 (3H, s), 6.18 (0.5H, s), 6.39 (0.5H, s), 6.62 (0.5H, d, J=9.8 Hz), 6.76 (0.5H, d, J=9.8 Hz), 6.95 (2H, d, J=7.8 Hz) 7.40 (2H, d, J=7.8 Hz), 7.28–7.40 (5H, m), and 7.42–7.48 (3H, m); HRMS (EI) Calcd for $C_{21}H_{18}O_3$ *m/z* 318.1256, found *m/z* 318.1230; IR (KBr) 3391, 2930, 1608, 1520, 1249, 1180 and 820 cm^{-1}; Anal. Calcd for $C_{21}H_{18}O_3$; C, 79.20%, H, 5.60%. Found C, 79.18%; H, 5.41%.

4.1.4. Benzyl 3-[3-(hydroxyphenylmethyl)-4′-methoxybiphenyl-4-yl]-acrylate (8). A mechanically stirred solution of **7** (610 mg, 1.9 mmol) and benzyl (triphenylphosphoranylidene) acetate (1.02 g, 2.48 mmol) in 20 ml of benzene was heated at 80°C for 1 h. The solvent was removed in vacuo. The residue was purified by a short silica gel column chromatography using CH_2Cl_2 as an eluent to give 815 mg of a colorless amorphous solid (95%). **8**: mp 133–135°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 (1H, s), 3.83 (3H, s), 5.21 (2H, s), 6.25 (1H, s), 6.33 (1H, d, J=15.6 Hz), 6.96 (2H, d, J=8.4 Hz), 7.54 (2H, d, J=8.4 Hz), 7.79 (1H, s), 7.38–7.24 (10H, m), 7.59 (1H, d, J=8.0 Hz), 7.48 (1H, d, J=8.0 Hz) and 8.11 (1H, d, J=15.6 Hz); HRMS (EI) Calcd for $C_{30}H_{26}O_4$ *m/z* 450.1855, found *m/z* 450.1830; IR (KBr) ν_{max} 3466, 3052, 3030, 2966, 1686, 1626, 1597, 1491, 1311, 1173, 825 and 705 cm^{-1}.

4.1.5. 3-(3-Benzyl-4′-methoxybiphenyl-4-yl)-propionic acid (9). A solution of **8** (680 mg, 1.5 mmol) in 20 ml of ethanol containing 10% palladium on activated carbon (200 mg) was stirred under hydrogen using a balloon for 36 h at room temperature. The catalyst was removed by filtration. The filtrate was evaporated under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc–hexane (1:1) as a eluent to give 490 mg of a colorless amorphous solid (94%). **9**: mp 121–123°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ2.50 (2H, t, J=8.7 Hz), 2.96 (2H, t, J=8.7 Hz), 3.83 (3H, s), 4.09 (2H, s), 6.95 (2H, d, J=8.9 Hz), 7.49 (2H, d, J=8.9 Hz), 7.15–7.27 (5H, m), 7.35 (1H, s), and 7.40 (1H, d, J=8.9 Hz); HRMS (EI) Calcd for $C_{23}H_{22}O_3$ *m/z* 346.1569 Found *m/z* 346.1581; IR (KBr) ν_{max} 3020, 2915, 2833, 1707, 1605, 1496, 1250 and 825 cm^{-1}.

4.1.6. 4-Benzyl-6-(4-methoxyphenyl)-indan-1-one (10). A stirred solution of **9** (200 mg, 0.58 mmol) and 0.4 ml of $SOCl_2$ in dry CH_2Cl_2 (1 ml) was heated at 60°C over 3 h. The mixture was evaporated in vacuo and the residue was redissolved in CH_2Cl_2 (2 ml). The crude acid chloride solution was added to a cooled solution (0°C) of $TiCl_4$ (0.126 ml, 1.16 mmol) in dry CH_2Cl_2 over 30 min. The mixture was stirred for 12 h below 5°C and then added into a rapidly stirred mixture of ice, 0.6 ml of conc. HCl and 2 ml CH_2Cl_2. After 15 min the mixture was partitioned and the aqueous layer was extracted with CH_2Cl_2. The organic layers were combined, washed successively with 3 M HCl, aqueous sat. $NaHCO_3$, and brine, and concentrated at reduced pressure. The residue was purified by silica gel column chromatography using CH_2Cl_2 as an eluent to give 85 mg of a colorless amorphous solid (50%). **10**: mp 79–81°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.69 (2H, t, J=6.8 Hz), 2.97 (2H, t, J=6.8 Hz), 3.82 (3H, s), 4.10 (2H, s), 6.95 (2H, d, J=8.9 Hz), 7.50 (2H, d, J=8.9 Hz), 7.16–7.28 (5H, m), 7.61 (1H, s) and 7.82 (1H, s); IR (KBr) ν_{max} 3040, 2980, 2960, 1709, 1609, 1519, 1474, 1250 and 827 cm^{-1}; HRMS (EI) Calcd for $C_{23}H_{20}O_2$ *m/z* 328.1463, found *m/z* 328.1463.

4.1.7. (*E*)-4-Benzyl-2-(4-methoxybenzylidene)-6-(4-methoxyphenyl)-indan-1-one (11). A solution of **10** (200 mg, 0.12 mmol), 2.5 M aqueous sodium hydroxide solution (5 ml, 12.5 mmol) and benzaldehyde (0.15 ml, 1.2 mmol) in 120 ml of 99.5% ethanol was stirred at room temperature for 24 h. The reaction mixture was cooled and filtered. The cake was washed with water until the alkali was entirely removed. The cake was dried to give 85 mg of a colorless amorphous solid (74%). **11**: mp 152–154°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83 (2H, s), 3.84 (3H, s), 3.86 (3H, s), 4.19 (2H, s), 6.97 (2H, d, J=8.0 Hz), 6.98 (2H, d, J=8.0 Hz), 7.55 (2H, d, J=8.0 Hz), 7.57 (2H, d, J=8.0 Hz), 7.18–7.34 (5H, m), 7.61 (1H, s), 7.65 (1H, s) and 7.98 (1H, s); HRMS (EI) Calcd for $C_{31}H_{26}O_3$ *m/z* 446.1882, found *m/z* 446.1893; IR (KBr) ν_{max} 3040, 2925, 1706, 1654, 1609, 1584, and 1251 cm^{-1}.

4.1.8. 4-Benzyl-2-(4-methoxybenzyl)-6-(4-methoxyphenyl)-indan-1-one (12). A solution of **11** (40 mg, 0.09 mmol) in a mixture of 99.5% ethanol (2 ml) and EtOAc (2 ml) containing 2 mg of platinum oxide was stirred in hydrogen atmosphere using a balloon. The mixture was

stirred at room temperature for 15 h. The catalyst was removed by filtration and the solvent was removed under reduced pressure. The residue was chromatographed on TLC plates (1:3 EtOAc–hexane) to give 28 mg of **12** as an oil (70%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.63–2.71 (2H, m), 2.95–3.05 (2H, m), 3.24–3.30 (1H, m), 3.79 (3H, s), 3.82 (3H, s), 4.03 (2H, s), 6.95 (2H, d, J=8.8 Hz), 6.97 (2H, d, J=8.8 Hz), 7.07–7.24 (5H, m), 7.24 (2H, d, J=8.8 Hz), 7.44 (2H, d, J=8.8 Hz), 7.58 (1H, s) and 7.83 (1H, s); HRMS (EI) Calcd for $C_{31}H_{28}O_3$ m/z 448.2039, found m/z 448.2046; IR (KBr) ν_{max} 3020, 2925, 1706, 1609, 1514, 1251, 1032 and 832 cm^{-1}.

4.1.9. 4-Benzyl-2-(4-hydroxybenzylidene)-6-(4-hydroxyphenyl)-indan-1-one (3a). To a solution of BBr_3 (0.12 ml of 1 M CH_2Cl_2 solution, 0.12 mmol) in 0.5 ml of dry CH_2Cl_2 at −78°C was added dropwise **12** (14 mg, 0.05 mmol) in 0.5 ml of dry CH_2Cl_2. After 5 h, the bath was removed and the reaction mixture was stirred at room temperature for 48 h. The reaction was quenched with water and the aqueous layer was separated and extracted with CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography to give 6.6 mg of a yellow oil (52%). **3a**: ^{1}H NMR (400 MHz, 9:1 $CDCl_3$–CD_3OD) δ 2.59–2.72 (2H, m), 2.96–3.05 (2H, m), 3.19–3.25 (1H, m), 4.03 (2H, s), 6.75 (2H, d, J=8.8 Hz), 6.90 (2H, d, J=8.8 Hz), 7.12–7.34 (5H, m), 7.00 (2H, d, J=8.8 Hz), 7.44 (2H, d, J=8.8 Hz), 7.59 (1H, s) and 7.79 (1H, s); IR (KBr) ν_{max} 3337, 2922, 1716, 1683, 1598, 1248 and 1172 cm^{-1}; HRMS (FAB) Calcd for (M+H) $C_{29}H_{25}O_3$ m/z 421.1820, found m/z 421.1804; Resolution of **3a** was performed on a HPLC DAICEL OC column (mobile phase: 2:1 hexane–EtOH, flow rate: 0.5 ml min^{-1}); (*S*)-**3a**: rt=20 min; (*R*)-**3a**: rt=24 min; (*S*)-**3a**: CD (EtOH) 263 nm (+7.4) 330 (0.0) 350 (−0.6); (*R*)-**3a**: CD (EtOH) 263 nm (7.4) 330 (0.0) 350 (+1.1).

4.1.10. 4-Benzyl-2-(4-hydroxybenzyl)-2-hydroxymethyl-6-(4-hydroxyphenyl)-indan-1-one (3b). A solution of **3a** (4 mg, 0.009 mmol), 2.5 M aqueous sodium hydroxide solution (0.01 ml, 0.025 mmol) and 37% formaldehyde solution (0.003 ml, 0.027 mmol) in 5 ml of 99.5% ethanol was stirred at room temperature for 2 h. The ethanol was removed in vacuo. The residue in CH_2Cl_2 was washed with aqueous HCl and dried over Na_2SO_4. The solvent was removed in vacuo. The residue was chromatographed on TLC plates (9:1 CH_2Cl_2–CH_3OH) to give 2.5 mg of an oil (60%).**3b**: ^{1}H NMR (400 MHz, 9:1 $CDCl_3$–CD_3OD)δ 2.80 (1H, d, J=14.8 Hz), 2.81 (1H, d, J=17.6 Hz), 2.94 (1H, d, J=17.6 Hz), 3.41 (1H, d, J=14.8 Hz), 3.81 (1H, d, J=10.4 Hz), 3.58 (1H, d, J=10.4 Hz), 4.20 (2H, s), 6.59 (2H, d, J=8.4 Hz), 6.81(2H, d, J=8.4 Hz), 6.88 (2H, d, J=8.4 Hz), 7.06–7.40 (5H, m), 7.41 (2H, d, J=8.4 Hz), 7.55 (1H, d, J=1.2 Hz) and 7.72 (1H, d, J=1.2 Hz), HRMS (EI) Calcd for $C_{30}H_{27}O_4$ m/z 451.1910 found m/z 451.1905 (M+1); Resolution of **3b** was performed on a HPLC DAICEL OC column (mobile phase: 6:1 hexane–EtOH, flow rate: 0.5 ml min^{-1}); (*S*)-**3b**: rt=33 min; (*R*)-**3b**: rt=38 min; (*S*)-**3b**: CD (EtOH) 263 nm (+10) 330 (0.0) 350 (−0.2); (*R*)-**3b** CD (EtOH) 263 nm (−10) 330 (0.0) 350 (+0.5); (*S*)-**3b**: $[\alpha]^{25}_D$=+110, (*c* 0.02, EtOH); (*R*)-**3b**: $[\alpha]^{25}_D$=−107, (*c* 0.02, EtOH).

4.1.11. 6-Trifluoromethanesulfonyloxyindan-1-one (14). To a solution of BBr_3 (25 ml of 1 M CH_2Cl_2 solution, 0.025 mol) in 50 ml of dry CH_2Cl_2 at −78°C was added dropwise **13** (2 g, 12 mmol, Aldrich) in 50 ml of dry CH_2Cl_2. After 5 h, the bath was removed and the reaction mixture was stirred at room temperature for 12 h. The reaction was quenched with water and the aqueous layer was extracted with CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, and concentrated in vacuo. The product was dissolved in 50 ml of dry CH_2Cl_2 at −78°C. Et_3N (1.6 g, 6.2 mmol) and DMAP (15 mg, cat.) were added to the solution. After complete dissolution had occurred, trifluoromethanesulfonic anhydride (1.6 g, 6.2 mmol) was added dropwise over 5 min. The solution was stirred at −78°C for 30 min then warmed to room temperature over 2 h. The reaction mixture was poured into saturated NH_4Cl solution (20 ml), the layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with water, dried over $MgSO_4$ and filtered. The solvent was removed in vacuo. The residue was pass though a short column of silicagel with CH_2Cl_2 to give 1.4 g of a red oil (87%). **14**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.78 (2H, t, J=6.0 Hz), 3.20 (2H, t, J=6.0 Hz), 7.64 (1H, d, J=2.0 Hz) 7.49 (1H, dd, J=8.4, 2.0 Hz) and 7.27 (1H, d, J=8.4 Hz); IR ($CHCl_3$) ν_{max} 1720, 1686, 1610, 1498, 1296 and 1144 cm^{-1}; HRMS (EI) Calcd for $C_{10}H_7O_4F_3S$ m/z 280.0017, found m/z 280.0018.

4.1.12. 6-(4-Methoxyphenyl)-indan-1-one (15). 14 (2.0 g, 5 mmol) was treated with 4-methoxyphenylboronic acid (1 g, 6 mmol), 2 M aqueous sodium carbonate solution (3 ml, 6 mmol), tetrakis(triphenylphosphine)palladium(0) (238 mg, 0.2 mmol) in a mixture of benzene (10 ml) and methanol (5 ml) at 80°C for 1 h. The solution was dried over Na_2SO_4 and evaporated. The residue was purified by silica gel column chromatography (CH_2Cl_2) to give 1 g of a white amorphous solid (86%). **15**: mp 139–141°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.74 (2H, t, J=6.0 Hz), 3.18 (2H, t, J=6.0 Hz), 3.87 (3H, s), 6.99 (2H, d, J=8.4 Hz), 7.54 (2H, d, J=8.4 Hz) 7.80 (1H, dd, J=8.4, 2.0 Hz) 7.93 (1H, d, J=2.0 Hz) and 7.52 (1H, d, J=8.4 Hz); HRMS (EI) Calcd for $C_{16}H_{14}O_2$ m/z 238.0993, found m/z 238.0987; IR ($CHCl_3$) ν_{max} 1702, 1608, 1482, 1269 and 828 cm^{-1}.

4.1.13. 2-(4-Methoxybezylidene)-6-(4-methoxyphenyl)-indan-1-one (16). A solution of **15** (560 mg, 2.3 mmol), 2.5 M aqueous sodium hydroxide solution (2.3 ml, 2.3 mmol) and benzaldehyde (0.15 ml, 1.2 mmol) in 150 ml of 99.5% ethanol was stirred at room temperature for 22 h. The reaction mixture was filtered. The cake was washed with water until the alkali was entirely removed. The cake was dried to give 630 mg of a colorless amorphous powder (75%). **16**: mp 129–131°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.87 (3H, s), 3.88 (3H, s), 4.05 (2H, s), 6.99 (4H, d, J=8.4 Hz), 7.58 (2H, d, J=8.4 Hz), 7.80 (1H, dd, J=8.4, 2.0 Hz), 8.09 (1H, d, J=2.0 Hz), 7.61 (1H, d, J=8.4 Hz), and 7.68 (1H, s); IR ($CHCl_3$) ν_{max} 1700, 1635, 1601, 1484 and 1268 cm^{-1}; Anal. Calcd for $C_{24}H_{20}O_3 \cdot 0.5H_2O$; C, 78.88; H, 5.79%. Found C, 79.11%; H, 5.43.

4.1.14. 2-(4-Methoxybenzyl)-6-(4-methoxyphenyl)-indan-1-one (17). A solution of **16** (200 mg, 0.56 mmol) in a

mixture of 99.5% ethanol (5 ml) and EtOAc (5 ml) containing 5 mg of platinum oxide was stirred in hydrogen atmosphere using a balloon at room temperature for 15 h. The catalyst was removed by filtration and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (CH_2Cl_2) to give 150 mg of a white amorphous solid (73%). **17**: mp 91–93°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.67 (1H, dd, J=7.8, 17.1 Hz), 3.17 (1H, dd, J=7.8, 17.1 Hz), 2.84 (1H, dd, J=4.2, 14.1 Hz), 3.34 (1H, dd, J=4.2, 14.1 Hz), 3.00 (1H, m), 3.78 (3H, s), 3.85 (3H, s), 6.84 (2H, d, J=8.4 Hz), 6.99 (2H, d, J=8.4 Hz), 7.79 (1H, dd, J=8.4, 2.0 Hz), 7.94 (1H, d, J=2.0 Hz), 7.56 (2H, d, J=8.4 Hz), 7.44(1H, d, J=8.4 Hz) and 7.18 (2H, d, J=8.4 Hz); IR ($CHCl_3$) ν_{max} 1705, 1609, 1582, 1490, 1301 and 1135 cm^{-1}; Anal. Calcd for $C_{24}H_{22}O_3 \cdot 0.5\ H_2O$; C, 78.45; H, 5.91. Found C, 78.17; H, 6.30.

4.1.15. 2-Hydroxymethyl-2-(4-methoxybenzyl)-6-(4-methoxyphenyl)-indan-1-one (18). A solution of **17** (100 mg, 0.27 mmol), 2.5 M aqueous sodium hydroxide solution (0.11 ml, 0.27 mmol) and 37% formaldehyde solution (0.025 ml, 0.27 mmol) in 5 ml of 99.5% ethanol was stirred at room temperature for 0.5 h. The solvent was removed in vacuo. The residue in CH_2Cl_2 was washed with aqueous HCl and dried over Na_2SO_4. The solvent was removed in vacuo. The residue was purified by silica gel chromatography (CH_2Cl_2) to give 80 mg of a white amorphous solid (77%). **18**: mp 91–93°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.92 (1H, d, J=17.8 Hz), 3.05 (2H, m), 3.16 (1H, d, J=17.8 Hz), 3.62 (1H, d, J=10.1 Hz), 3.85 (1H, d, J=10.1 Hz), 3.76 (3H, s), 3.84 (3H, s), 6.73 (2H, d, J=9.0 Hz), 6.98 (2H, d, J=9.0 Hz), 7.07 (2H, d, J=9.0 Hz), 7.41 (1H, d, J=9.0 Hz), 7.52 (2H, d, J=9.0 Hz), 7.75 (1H, dd, J=9.0, 1.8 Hz) and 7.87 (1H, d, J=1.8 Hz); HRMS (FAB) Calcd for $C_{25}H_{25}O_4$ (M+H) m/z 389.1753, found m/z 389.1754; IR ($CHCl_3$) ν_{max} 2932, 1702, 1611, 1513, 1250 and 1036 cm^{-1}.

4.1.16. 2-Hydroxymethyl-2-(4-methoxybenzyl)-6-(4-methoxyphenyl)indan-1-ol (19). To a solution of **18** (75 mg, 0.19 mmol) in 1 ml of 99.5% ethanol solution was added dropwise $NaBH_4$ (21 mg, 0.57 mmol) suspend in 1 ml of THF at 0°C. The reaction mixture was stirred at 4°C for 12 h. The mixture was quenched with water and aqueous layer and extracted with CH_2Cl_2. The organic layers were combined and dried over Na_2SO_4. The solvent was removed in vacuo. The residue was purified by silica gel column chromatography (CH_2Cl_2) to give diol **19** (40 mg) and its diastereomers (28 mg). **19**: mp 80–82°C; ^{1}H NMR (400 MHz, 9:1 $CDCl_3$–CD_3OD) δ 2.34 (1H, d, J=16.0 Hz), 2.49 (1H, d, J=12.4 Hz), 2.81 (1H, d, J=16.0 Hz), 3.10 (1H, d, J=12.4 Hz), 3.45 (1H, d, J=10.4 Hz), 3.62 (1H, d, J=10.4 Hz), 3.75 (3H, s), 3.80 (3H, s), 5.22 (1H, s) 6.84 (2H, d, J=8.8 Hz), 6.98 (2H, d, J=8.8 Hz), 7.14 (1H, d, J=8.8 Hz), 7.22 (1H, d, J=7.8 Hz), 7.48 (1H, d, J=7.8 Hz), 7.54(2H, d, J=8.8 Hz) and 7.59 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.8, 53.8, 55.2, 55.3, 66.1, 80.5, 114.1, 113.4, 122.5, 125.1, 126.6, 128.0, 130.6, 131.5, 133.9, 138.8, 139.6, 144.7, 157.9 and 158.9 ppm; IR ($CHCl_3$) ν_{max} 3422, 1610, 1511 and 1248 cm^{-1}; resolution of **19** was performed on a HPLC DAICEL OC column (mobile phase: 1:1 hexane–EtOH, flow rate: 1.0 ml min^{-1}); (*S*)-**19**: rt=9 min; (*R*)-**19**: rt=7 min; (*R*)-**19** $[\alpha]^{25}_D$=−55, (*c* 0.02, EtOH); Anal. Calcd for $C_{25}H_{26}O_4 \cdot 0.8H_2O$; C,74.16%; H, 6.87%. Found C, 74.38%; H, 6.83%.

4.2. Compound (*R*)-18

A solution of (−)-**19** (1 mg, 0.003 mmol), MnO_2 (1 mg, excess) in 0.5 ml of THF solution was stirred at room temperature for 1 h. The solvent was removed in vacuo. The residue was purified by silica gel plate (CH_2Cl_2) to give 0.76 mg (75%) of (*R*)-**18**. $[\alpha]^{25}_D$=−91, (*c* 0.04, EtOH); ^{1}H NMR was same as (±)-**18**; CD (EtOH) 263 nm (−11) 330 (0.0) 350 (0.2).

4.2.1. Di-4-dimethylaminobenzoate 20. A mixture solution of (+)-**19** (10 mg, 0.025 mmol), 4-dimethylaminobenzoyl chloride in 0.5 ml of pyridine was stirred at 110°C for 24 h. The mixture was quenched with water and aqueous layer was extracted with CH_2Cl_2. The organic layer was combined and dried over Na_2SO_4. The solvent was removed in vacuo. The residue was purified on a silica gel plate to give 2.5 mg of **20** as a yellow oil (20%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.64 (1H, d, J=16 Hz), 2.98 (6H, s), 3.02 (6H, s), 3.23 (2H, d, J=16 Hz), 3.75 (3H, s), 3.81 (3H, s), 3.76–3.83 (1H, m), 4.04 (1H, d, J=10 Hz), 4.16 (1H, d, J=10 Hz), 6.52 (2H, d, J=8.8 Hz), 6.6 (1H, s), 6.64 (2H, d, J=8.8 Hz), 6.77 (2H, d, J=8.8 Hz), 6.91 (2H, d, J=8.8 Hz), 7.08 (2H, d, J=8.8 Hz), 7.25 (1H, d, J=8.0 Hz), 7.44 (1H, d, J=8.0 Hz), 7.47 (2H, d, J=8.8 Hz), 7.81 (2H, d, J=8.8 Hz), 7.98 (2H, d, J=8.8 Hz), and 7.61 (1H, s); HRMS (EI) Calcd for $C_{43}H_{44}O_6N_2$ m/z 684.3200, found m/z 684.3215; IR ($CHCl_3$) ν_{max} 1701, 1608, 1278 and 1183 cm^{-1}; $[\alpha]^{22}_D$=+51 (*c* 0.02, EtOH).

4.2.2. 2-(4-Hydroxy-benzyl)-2-hydroxymethyl-6-(4-hydroxyphenyl)-indan-1-one (3c). To a solution of BBr_3 (0.15 ml, 0.15 mmol) in 5 ml of dry CH_2Cl_2 at −78°C was added dropwise **17** (50 mg, 0.14 mmol) in 5 ml of dry CH_2Cl_2. After 3 h, the bath was removed and the reaction mixture was stirred at room temperature for 15 h. The reaction was quenched with water and the aqueous layer was extracted with CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, and concentrated in vacuo. A solution of the crude product (36 mg, 0.11 mmol), 2.5 M aqueous sodium hydroxide solution (0.044 ml, 0.11 mmol) and 37% formaldehyde solution (0.01 ml, 0.11 mmol) in 2 ml of 99.5% ethanol was stirred at room temperature for 0.5 h. The solvent was removed in vacuo. The residue in CH_2Cl_2 was washed with aqueous HCl and dried over Na_2SO_4. The solvent was removed in vacuo. The residue was purified by silica gel chromatography (CH_2Cl_2) to give 36 mg of a white amorphous solid (60% in two steps). **3c**: mp 91–93°C; ^{1}H NMR (300 MHz, 9:1 $CDCl_3$–CD_3OD) 2.87 (1H, d, J=13.5 Hz), 2.94 (1H, d, J=13.5 Hz), 2.95 (1H, d, J=16 Hz), 3.15 (1H, d, J=16 Hz), 3.61 (1H, d, J=10.8 Hz), 3.84 (1H, d, J=10.8 Hz), 6.66 (2H, d, J=8.4 Hz), 7.00 (2H, d, J=8.4 Hz), 6.88 (2H, d, J=8.4 Hz), 7.42 (2H, d, J=8.4 Hz), 7.39 (1H, d, J=8.1 Hz), 7.71 (1H, d, J=8.1 Hz) and 7.82 (1H, s); HRMS (EI) Calcd for $C_{23}H_{20}O_4$ m/z 360.1362, found m/z 360.1389; IR ($CHCl_3$) ν_{max} 3278, 2918, 1691, 1662, 1614, 1514, 1485, 1479, 1440, 1276 and 1223 cm^{-1}; Resolution of **3c** was performed on a

HPLC DAICEL OC column (mobile phase: 3:1 hexane–EtOH, flow rate: 1 ml min^{-1}); (*S*)-**3c**: rt=16 min; (*R*)-**3c**: rt=18 min; (*S*)-**3c**: $[\alpha]^{25}_{D}$=+65, (*c* 0.02, EtOH); CD (EtOH) 265 nm (+13) 330 (0.0) 350 (−0.6); (*R*)-**3c**: $[\alpha]^{25}_{D}$=−39, (*c* 0.04, EtOH); CD (EtOH) 265 nm (−10) 330 (0.0) 350 (0.4).

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