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Tetrahedron
Tetrahedron 63 (2007) 4459–4463

# Synthesis of a selective estrogen receptor β-modulator via asymmetric phase-transfer catalysis

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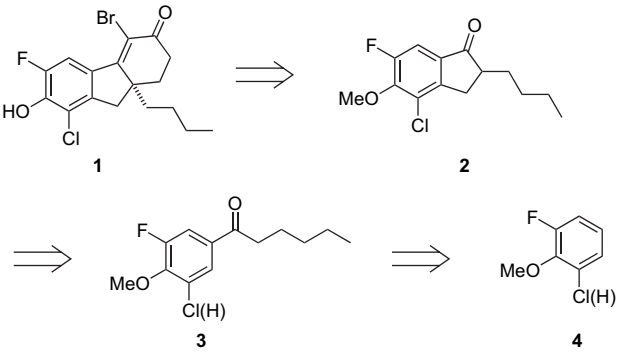
Received 24 January 2007; revised 5 March 2007; accepted 12 March 2007
Available online 16 March 2007

**Abstract**—An efficient asymmetric synthesis of selective estrogen receptor β-modulator (*S*)-4-bromo-9a-butyl-8-chloro-6-fluoro-7-hydroxy-1,2,9,9a-tetrahydro-fluoren-3-one was developed. The route features a chemoselective aromatic chlorination reaction, an asymmetric phase-transfer-catalyzed alkylation of an indanone with efficient ee upgrade by racemate crystallization, and a robust bromination reaction using imidazole as an in situ bromine trap to avoid overreaction. The synthesis proceeds in 34% yield over 8 steps from 2-fluoroanisole, and provides material with >99.5% ee.


## 1. Introduction

Hormone replacement therapy (HRT) has been a widely used and effective treatment for the symptoms of menopause.[1] However the Women's Health Initiative[2] identified adverse effects associated with chronic HRT, which highlight the need for improved therapies. The discovery of two estrogen receptor subtypes (α and β)[3] with different tissue distributions[4] raises the possibility that subtype-specific estrogen receptor modulators might avoid some of the adverse effects of non-selective HRT. A program to identify β-selective ligands[5] led to the identification of tetrahydrofluorenones including **1** as potent and subtype-selective estrogen receptor β-modulators.[6] This paper presents the development of an asymmetric synthesis of **1** that allowed for the preparation of larger quantities to support advanced preclinical studies.

Racemic syntheses of **1** and related tetrahydrofluorenones have been achieved through Robinson annulation of 2-substituted-5-methoxy indanones.[5a,6,7] In one case, targeting a candidate for brain edema treatment, extension of the catalytic asymmetric phase-transfer alkylation of indanones to alkylation with 1,3-dichloro-2-butene led to an efficient asymmetric Robinson annulation.[8] Although the substrate scope of the asymmetric annulation had not been defined, this reaction might form the basis of an attractive approach to **1** (Scheme 1).




**Scheme 1**.

The required methoxy indanone **2** could be accessed by a Friedel–Crafts acylation/alkylation sequence, and a late-stage bromination and deprotection would complete the synthesis.

## 2. Results and discussion

The route used during drug discovery[6] began with Friedel–Crafts acylation of 1-chloro-6-fluoroanisole (**4a**) with hexanoyl chloride (Scheme 2). This reaction was sluggish due to the electron deficiency of **4a**; cleavage of the *O*-methyl group followed by O-acylation of the resulting phenol competed with the desired reaction. Reaction of the product **3a** with formaldehyde in methanol gave a mixture of methoxymethyl and methylene substituted products **5a** and **6a**. Acid-catalyzed intramolecular alkylation was only moderately regioselective, giving indanones **2** and **7a** in a ratio of 85:15.

*Keywords*: Phase-transfer catalysis; Asymmetric catalysis; Bromination; Chlorination.
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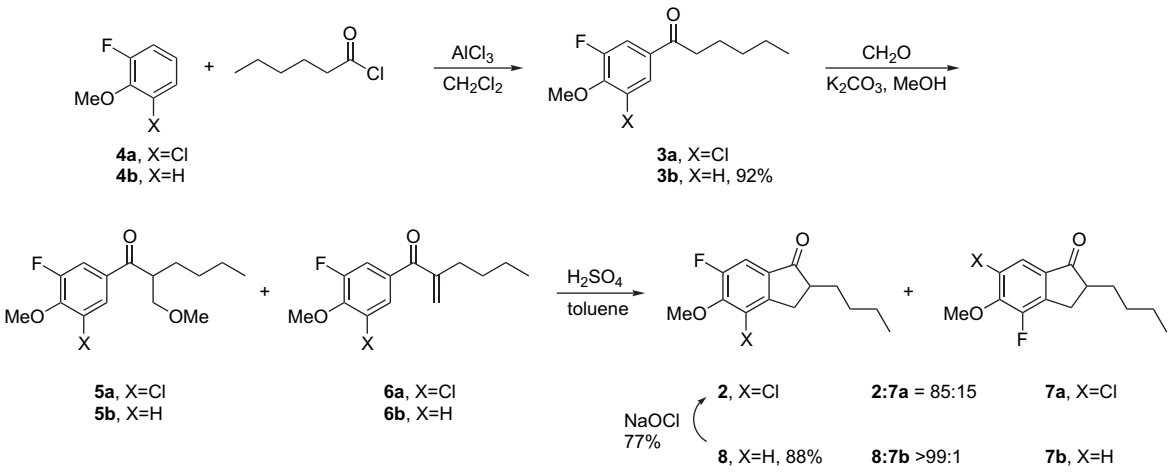
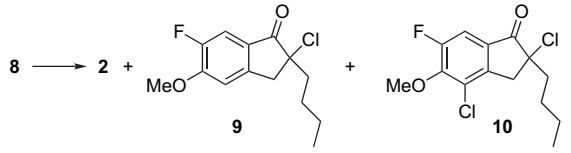
doi:10.1016/j.tet.2007.03.074




**Scheme 2**.

To address these issues, we began our synthesis with 2-fluoroanisole (**4b**). Friedel–Crafts acylation was facile and highly para-selective, and **3b** was crystallized in 92% yield. After reaction with formaldehyde to give the mixture of **5b** and **6b**, intramolecular aromatic substitution occurred away from the fluorine substituent, giving indanone **8** with complete regioselectivity and 88% yield after crystallization.

At this stage, selective chlorination of **8** was required. In addition to the aromatic 4-position of indanone, the 2-position $\alpha$ to the ketone, the benzylic 3-position and the aromatic 6-position were all potential sites for reactivity with a chlorine source. In practice, only reaction at $\alpha$ to the carbonyl competed with the desired 4 chlorination (Scheme 3).

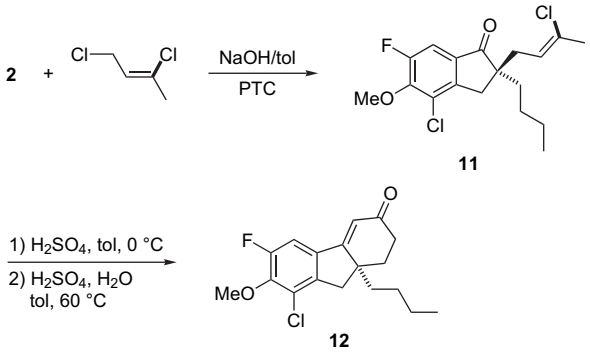



**Scheme 3**.

Sulfuryl chloride, NCS, and dichlorodimethyl hydantoin all reacted selectively at the 2-position to give undesired **9** under anhydrous conditions. In the presence of aqueous acid, the two *N*-chloro reagents also reacted at the 4-position giving some desired **2** and dichloro derivative **10**. *tert*-Butyl hypochlorite in acetic acid gave good selectivity toward **2**. Similar selectivity was seen with aqueous sodium hypochlorite in acetic acid and with gaseous chlorine in aqueous acetic acid. Both NaOCl and $Cl_2$ favored **9** and **10** under non-acidic conditions.

The most practical procedure involved addition of aqueous NaOCl to a solution of **8** in acetic acid. The product was crystallized from the reaction mixture and could be isolated directly in 77% yield.

The key asymmetric alkylation of **2** with 1,3-dichloro-2-butene was initially tried under the literature conditions, using 10% *N*-(*p*-trifluoromethylbenzyl)cinchoninium bromide as catalyst (Scheme 4). The desired (*S*) enantiomer was obtained as expected,[8,9] but in only 65% ee compared with 92% ee previously obtained for alkylation of 6,7-dichloro-5-methoxy-2-propyl-1-indanone. The reaction was optimized by reducing the catalyst charge to 5%, reducing the large excess of dichlorobutene to a charge of 1.25 equiv, and running the alkylation at 10 °C for 30 h, which gave a 95% yield and 76% ee. A further improvement to 80% ee was possible by running the reaction under very dilute conditions (100 mL toluene/g indanone), but this was impractical for larger scale use.

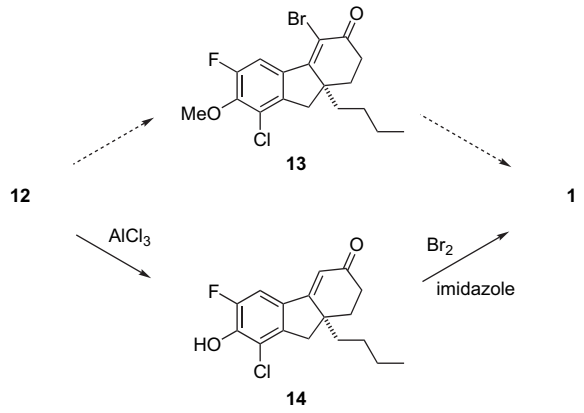



**Scheme 4**.

A few other cinchona-based phase-transfer catalysts were evaluated without improvement in selectivity. It is noteworthy that *N*-(9-anthracenylmethyl)-dihydrocinchoninium bromide and *O*-(9)-allyl-*N*-(9-anthracenylmethyl)-cinchonidinium bromide catalysts, which carry out highly enantioselective alkylations of *tert*-butylglycinate benzophenone imine,[10] were poorly selective in the alkylation of indanone **2**, providing a maximum ee of 26%.

Cyclization of alkylation product **11** to the tetrahydrofluorenone **12** was accomplished with sulfuric acid and water in toluene.[8] The enantiomeric purity of **12** could be increased to 97% ee by crystallization of the insoluble racemate from heptane. In practice, however, the upgrade was deferred to a later stage where it was found to be even more efficient (vide infra).

Conversion of **12** to the final product **1** required installation of the bromine atom and cleavage of the phenolic methyl group (Scheme 5). In the original synthesis,[6] bromination was performed first to give racemic **13**, which was resolved by chromatography. Deprotection with $BBr_3$ then gave **1**. The drawback for large-scale asymmetric synthesis was that **13**, like **12**, was only crystalline in racemic form. In contrast, deprotection of **12** with $AlCl_3$ gave free phenol **14**, which could be crystallized. We felt that isolation at this stage would provide valuable purification prior to the final step. Racemic **14** is extremely insoluble, and the enantiomeric purity was upgraded to 99% ee by filtration of the quenched reaction mixture prior to crystallization of the (*S*) isomer from acetonitrile. Compound **14** was obtained in 61% yield over the three steps from indanone **2** with 23% having been removed as racemate.




**Scheme 5**.

Bromination to give **1** could be carried out by addition of precisely 1 equiv of bromine to a mixture of **14** and sodium acetate in ethanol/acetic acid. Addition of water then crystallized the product. Stoichiometry was critical because any excess bromine catalyzed formation of a dimeric by-product.[11] On the other hand, if less than 0.995 equiv of bromine was added, the remaining **14** was not adequately removed in the crystallization. Each of these scenarios required a different recrystallization procedure to achieve target purity.

The fact that the dimeric impurity forms only after all of **14** is consumed indicates that this side reaction is significantly slower than the consumption of bromine in the formation of **1**. This raises the possibility that a bromine trapping reagent of intermediate reactivity might be used to prevent the side reaction without interfering with the desired bromination. About 20 potential bromine traps were evaluated, including olefinic, aromatic, and heteroaromatic compounds. From these experiments, imidazole emerged as having the appropriate rate of reactivity. Imidazole has the additional benefit of the proper basicity to replace sodium acetate in the role of base for the bromination reaction, which liberates HBr. Under the optimized conditions, 1.75 equiv of imidazole are combined with **14** in ethanol/acetic acid and bromine is added slowly. One equivalent of bromine is sufficient for complete conversion, but excess can be used and is converted to mono- and polybromo imidazoles. Addition of water crystallizes **1** in 90% yield, or 88% after a decolorizing carbon treatment.

## 3. Conclusion

Selective estrogen receptor β-modulator **1** was synthesized in eight steps and 34% overall yield, starting from 2-fluoroanisole. The synthesis features a chemoselective aromatic chlorination reaction, an asymmetric phase-transfer-catalyzed alkylation with efficient ee upgrade by racemate crystallization, and a robust bromination reaction, which uses imidazole as an in situ bromine trap to avoid overreaction. The route was used to prepare kilogram quantities of **1** to allow for advanced preclinical studies.

## 4. Experimental

### 4.1. General methods

All reactions were conducted under an atmosphere of dry nitrogen. All reagents and solvents are available from commercial sources and were used as received unless otherwise indicated. 1,3-Dichloro-2-butene was prepared according to a method described in a patent.[12] Dichloromethane and toluene were dried over 4 Å molecular sieves. $^1$H NMR and $^{13}$C NMR spectra were recorded at 400 MHz and 100 MHz, respectively. Chemical shifts are referenced to solvent signals (proton $\delta$ 7.27 for $CHCl_3$, carbon $\delta$ 77.0 for $CDCl_3$).

**4.1.1. 1-(3-Fluoro-4-methoxyphenyl)hexan-1-one (3b).** To a solution of 2-fluoroanisole (158 g, 1250 mmol) in dry dichloromethane (1.25 L) was added $AlCl_3$ (196 g, 1470 mmol). The solution was then cooled on a water bath while hexanoyl chloride (194 g, 1440 mmol) was added dropwise. The resulting solution was stirred for 30 min at room temperature, then cooled to −10 °C. Water (1.25 L) was added slowly to quench. *Caution:* quenching is highly exothermic. The organic layer was separated and washed with aqueous 5 N NaOH (625 mL) followed by water (625 mL). The final organic layer was evaporated to low volume and the residue was dissolved in hot heptane (850 mL). Crystallization occurred during cooling and the solid was collected at 0 °C, rinsing with cold heptane. Drying under vacuum gave **3b** as white crystals (258 g, 92%). Mp 61–62 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.74 (m, 1H), 7.69 (dd, $J$=12.0, 2.1 Hz, 1H), 6.99 (t, $J$=8.4 Hz, 1H), 3.95 (s, 3H), 2.87 (t, $J$=7.4 Hz, 2H), 1.72 (m, 2H), 1.35 (m, 4H), 0.91 (m, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 198.3, 152.1 (d, $J$=248 Hz), 151.7 (d, $J$=11 Hz), 130.5 (d, $J$=5 Hz), 125.3 (d, $J$=3 Hz), 115.8 (d, $J$=19 Hz), 112.4 (d, $J$=1 Hz), 56.3, 38.3, 31.6, 24.2, 22.6, 14.0. Anal. Calcd for $C_{13}H_{17}FO_2$: C, 69.62; H, 7.64. Found: C, 69.79; H, 7.68.

**4.1.2. 1-(3-Fluoro-4-methoxyphenyl)-2-methoxymethylhexan-1-one (5b) and 1-(3-fluoro-4-methoxyphenyl)-2-methylenehexan-1-one (6b).** To a solution of **3b** (253 g, 1130 mmol) in methanol (1.13 L) were added $K_2CO_3$ (156 g, 1130 mmol) and aqueous 37% formaldehyde (110 g, 1355 mmol). The suspension was stirred at 50 °C for 18 h, and then cooled to room temperature. Toluene (1.13 L) and water (1.13 L) were added and the layers were separated. The organic layer was washed again with water (1.13 L), and then concentrated to a volume of 500 mL. The solution was used in the next step without further

purification. NMR data were acquired on the mixture. Compound **5b**: $^1$H NMR ($CDCl_3$) $\delta$ 7.78 (ddd, $J$=8.3, 2.0, 0.8 Hz, 1H), 7.74 (dd, $J$=12.0, 2.0 Hz, 1H), 7.01 (t, $J$=8.3 Hz, 1H), 3.96 (s, 3H), 3.71–3.61 (m, 2H), 3.49 (q, $J$=3.8 Hz, 1H), 3.29 (s, 3H), 1.71 (m, 1H), 1.51 (m, 1H), 1.27 (m, 4H), 0.85 (t, $J$=7.2 Hz, 3H). Compound **6b**: $^1$H NMR ($CDCl_3$) $\delta$ 7.62 (ddd, $J$=8.4, 2.1, 1.0 Hz, 1H), 7.59 (dd, $J$=12.0, 2.1 Hz, 1H), 6.99 (t, $J$=8.4 Hz, 1H), 5.75 (q, $J$=1.2 Hz, 1H), 5.50 (s, 1H), 3.97 (s, 3H), 2.46 (t, $J$=7.4 Hz, 2H), 1.38 (m, 2H), 1.27 (m, 2H), 0.93 (t, $J$=7.2 Hz, 3H).

**4.1.3. 2-Butyl-6-fluoro-5-methoxyindan-1-one (8).** The solution of **5b** and **6b** in toluene (estimated 1130 mmol combined with 500 mL) was diluted with toluene (2 L). Concentrated sulfuric acid (250 mL) was added and the two-phase mixture was stirred at 50 °C for 3 h. The mixture was then cooled to 5 °C and slowly quenched with water (1.25 L), maintaining the temperature below 20 °C. Layers were separated and the organic layer was washed again with water (1.25 L). The final toluene solution was concentrated to low volume and the residue was dissolved in hot heptane (1 L). The product crystallized upon cooling and was isolated by filtration at 0 °C, rinsing with cold heptane/toluene 9:1. Drying under vacuum gave **8** as off-white crystals (231 g, 88%). Mp 82–83 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.38 (d, $J$=9.8 Hz, 1H), 6.94 (d, $J$=7.2 Hz, 1H), 3.96 (s, 3H), 3.24 (dd, $J$=17.0, 7.7 Hz, 1H), 2.74 (br d, $J$=17.0 Hz, 1H), 2.64 (m, 1H), 1.92 (m, 1H), 1.48–1.29 (m, 5H), 0.90 (t, $J$=7.1 Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 207.0 (d, $J$=3 Hz), 153.9 (d, $J$=20 Hz), 152.6 (d, $J$=252 Hz), 151.3 (d, $J$=5 Hz), 129.6 (d, $J$=6 Hz), 110.1 (d, $J$=18 Hz), 109.3 (d, $J$=1 Hz), 56.4, 47.9, 32.8, 31.3, 29.5, 22.8, 14.0. Anal. Calcd for $C_{14}H_{17}FO_2$: C, 71.16; H, 7.25. Found: C, 71.28; H, 7.35.

**4.1.4. 2-Butyl-4-chloro-6-fluoro-5-methoxyindan-1-one (2).** A solution of **8** (140 g, 593 mmol) in glacial acetic acid (1.77 L) was cooled to 16 °C in a water bath. Aqueous 7.57% NaOCl (1.14 kg, 1160 mmol) was added dropwise over 4 h. Water (800 mL) was then added over 30 min to complete the crystallization. The suspension was filtered, rinsing with 1:1 AcOH/water, water, and finally with methanol/water 2:1. Drying under vacuum gave **2** as an off-white solid (124 g corrected for 99% purity, 77%). An analytically pure sample was obtained by recrystallization from methanol. Mp 56–57 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.39 (d, $J$=9.5 Hz, 1H), 4.09 (d, $J$=2.4 Hz, 3H), 3.27 (qd, $J$=9.8, 1.4 Hz, 1H), 2.76–2.66 (m, 2H), 1.94 (m, 1H), 1.52–1.33 (m, 5H), 0.93 (t, $J$=7.1 Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 206.4, 155.7 (d, $J$=252 Hz), 149.8 (d, $J$=14 Hz), 148.4, 132.2 (d, $J$=7 Hz), 125.6 (d, $J$=4 Hz), 109.8 (d, $J$=20 Hz), 61.6 (d, $J$=7 Hz), 47.5, 31.8, 31.2, 29.4, 22.7, 14.0. Anal. Calcd for $C_{14}H_{16}ClFO_2$: C, 62.11; H, 5.96. Found: C, 62.22; H, 5.98.

**4.1.5. 2-Butyl-2-chloro-6-fluoro-5-methoxyindan-1-one (9).** To a solution of **8** (118 mg, 0.50 mmol) in acetic acid (0.5 mL) was added sulfuryl chloride (74 mg, 0.55 mmol). After 90 min, the reaction was quenched with water and extracted with ethyl acetate. The organic layer was washed twice with water and evaporated to a yellow oil (118 mg, 87%). $^1$H NMR ($CDCl_3$) $\delta$ 7.50 (d, $J$=9.5 Hz, 1H), 6.93 (d, $J$=7.0 Hz, 1H), 3.99 (s, 3H), 3.46 (s, 2H), 2.10 (m, 1H), 1.91 (m, 1H), 1.52 (m, 1H), 1.42–1.25 (m, 3H), 0.92 (t, $J$=7.2 Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 198.7, 155.1 (d, $J$=12 Hz), 152.9 (d, $J$=251 Hz), 148.1, 126.1 (d, $J$=6 Hz), 111.3 (d, $J$=19 Hz), 109.2, 71.0, 56.5, 42.9, 38.4, 26.8, 22.7, 13.9. Anal. Calcd for $C_{14}H_{16}ClFO_2$: C, 62.11; H, 5.96. Found: C, 62.09; H, 6.00.

**4.1.6. 2-Butyl-2,4-dichloro-6-fluoro-5-methoxyindan-1-one (10).** To a solution of **8** (59 mg, 0.25 mmol) in acetonitrile (0.5 mL) was added NCS (91 mg, 0.68 mmol) and conc HCl (42 μL). After stirring for 48 h, the mixture was partitioned between ethyl acetate and water. The organic layer was washed with water and aqueous 5% $NaHCO_3$, then diluted with an equal volume of heptane and filtered through a pad of silica gel. Evaporation gave an oil (68 mg, 89%). $^1$H NMR ($CDCl_3$) $\delta$ 7.50 (d, $J$=9.6 Hz, 1H), 4.13 (d, $J$=2.8 Hz, 3H), 3.44 (m, 2H), 2.14 (m, 1H), 1.91 (m, 1H), 1.56 (m, 1H), 1.43–1.25 (m, 3H), 0.93 (t, $J$=7.2 Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 198.2, 155.8 (d, $J$=253 Hz), 150.8 (d, $J$=14 Hz), 145.1 (d, $J$=2 Hz), 128.7 (d, $J$=7 Hz), 125.4 (d, $J$=4 Hz), 111.4 (d, $J$=21 Hz), 70.0, 61.7 (d, $J$=7 Hz), 41.9, 38.1, 26.8, 22.7, 13.9. HRMS calcd for $C_{14}H_{15}Cl_2FO_2$: 305.0511 (M+H). Found: 305.0518 (M+H).

**4.1.7. (*S*)-2-Butyl-4-chloro-2-(3-chlorobut-2-enyl)-6-fluoro-5-methoxyindan-1-one (11).** To a solution of **2** (92.5 g, 342 mmol) in toluene (1.4 L) was added *N*-[4-(trifluoromethyl)-benzyl]cinchoninium bromide (9.1 g, 17 mmol). Aqueous 50% NaOH (465 mL) was added and the mixture was cooled to 10 °C. 1,3-Dichloro-2-butene (534 g, 427 mmol, mixture of *Z* and *E* isomers) was then added and the mixture was vigorously stirred for 30 h. The reaction was then quenched by slow addition of water (1.4 L), which raised the temperature to 20 °C. The aqueous layer was removed. The organic layer was washed with water (450 mL) followed by 1 M citric acid (450 mL). The final toluene layer was filtered to remove a small amount of precipitate, then concentrated to a volume of 500 mL. The crude solution was used directly in the next step. $^1$H NMR ($CDCl_3$) (signals reported for major *Z* isomer) $\delta$ 7.39 (d, $J$=9.6 Hz, 1H), 5.29 (m, 1H), 4.11 (d, $J$=2.4 Hz, 3H), 2.92 (d, $J$=1.5 Hz, 2H), 2.50 (qdd, $J$=14.9, 6.8, 1.4 Hz, 2H), 2.35 (br d, $J$=8.0 Hz, 1H), 2.05 (d, $J$=1.2 Hz, 3H), 1.64 (m, 3H), 1.30–0.98 (m, 4H), 0.85 (t, $J$=7.2 Hz, 3H).

**4.1.8. (*S*)-9a-Butyl-8-chloro-6-fluoro-7-methoxy-1,2,9,9a-tetrahydrofluoren-3-one (12).** The solution of **11** (325 mmol) in toluene (500 mL) was cooled to 0 °C with an ice bath. Concentrated $H_2SO_4$ (350 mL) was added over 1 h. *Caution:* addition is exothermic and HCl is liberated. The mixture was stirred for 1 h more at 35 °C. Water (11 mL) was then added and the mixture was heated to 65 °C for 2 h. The mixture was then cooled to 20 °C and slowly added into cold water (750 mL). The layers were separated and the organic layer was washed with aqueous 5% $NaHCO_3$ (500 mL). Assays showed 105 g (95% from **2**) and 76% ee. The toluene solution was carried into the next step. A small sample of racemic **12** was collected by evaporation of the toluene solution and crystallization from heptane. $^1$H NMR ($CDCl_3$) $\delta$ 7.19 (d, $J$=10.1 Hz, 1H), 6.10 (s, 1H), 4.02 (d, $J$=1.8 Hz, 3H), 3.08 (d, $J$=16.7 Hz, 1H), 2.66 (d, $J$=16.7 Hz, 1H), 2.61–2.43 (m, 2H), 2.31 (ddd, $J$=13.2, 5.1, 1.9 Hz, 1H), 1.98 (td, $J$=13.2, 5.6 Hz, 1H),

1.62 (m, 1H), 1.46 (m, 1H), 1.31–1.17 (m, 4H), 0.86 (t, $J$=7.0 Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 198.6, 171.5 (d, $J$=3 Hz), 155.8 (d, $J$=249 Hz), 147.0 (d, $J$=14 Hz), 141.8 (d, $J$=2 Hz), 133.5 (d, $J$=9 Hz), 125.4 (d, $J$=4 Hz), 117.5, 109.1 (d, $J$=21 Hz), 61.7 (d, $J$=6 Hz), 46.5, 42.4, 37.5, 33.8, 31.9, 27.5, 23.2, 14.0. Anal. Calcd for $C_{18}H_{20}ClFO_2$: C, 66.97; H, 6.24. Found: C, 67.00; H, 6.25.

**4.1.9. (*S*)-9a-Butyl-8-chloro-6-fluoro-7-hydroxy-1,2,9,9a-tetrahydrofluoren-3-one (14).** A toluene solution of **12** (30.0 g, 92.9 mmol, 76% ee) was azeotropically dried and concentrated to a volume of 170 mL. The solution was cooled to 5 °C and $AlCl_3$ (18.6 g, 139 mmol) was added. Once the exotherm subsided, the mixture was warmed to 40 °C for 2.5 h. The reaction was then quenched at 40 °C by slow addition of 1-propanol (29 mL). The mixture was stirred for 1 h more at 45 °C, and then cooled to 20 °C. A pre-mixed combination of aqueous 10% citric acid (310 mL) and aqueous 2 N HCl (35 mL) was added, very slowly at first with cooling to keep the temperature between 20 and 50 °C. The mixture was then stirred for 1 h more at 20 °C. The precipitated racemate was removed by filtration, rinsing with 5% 1-propanol in toluene. The filtrate was allowed to settle and the aqueous layer was removed. The organic layer was washed again with the aqueous citric acid/HCl mixture (225 mL) followed by 0.1 N HCl (225 mL), adding 1-propanol (14 mL) to the organic phase before each wash. The final toluene solution was evaporated with simultaneous addition of acetonitrile until toluene was removed and the final volume was 132 mL. The mixture was heated to 55 °C, and then cooled slowly to induce crystallization. The solid was collected at −20 °C, rinsing with cold acetonitrile. Drying under vacuum gave **14** as a tan solid (18.23 g, 64%, 99% ee). Mp 121–122 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.49 (br s, 1H), 7.21 (d, $J$=9.3 Hz, 1H), 6.12 (s, 1H), 3.08 (d, $J$=16.7 Hz, 1H), 2.68 (d, $J$=16.7 Hz, 1H), 2.64–2.47 (m, 2H), 2.31 (ddd, $J$=13.2, 5.1, 1.9 Hz, 1H), 2.00 (td, $J$=13.2, 5.7 Hz, 1H), 1.63 (m, 1H), 1.47 (m, 1H), 1.31–1.16 (m, 4H), 0.86 (t, $J$=7.0 Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 199.7, 173.2, 151.5 (d, $J$=245 Hz), 144.4 (d, $J$=16 Hz), 142.1 (d, $J$=2 Hz), 129.9 (d, $J$=8 Hz), 119.0 (d, $J$=4 Hz), 116.3, 108.4 (d, $J$=20 Hz), 46.6, 42.3, 37.7, 33.7, 31.9, 27.6, 23.2, 14.0. Anal. Calcd for $C_{17}H_{18}ClFO_2$: C, 66.13; H, 5.88. Found: C, 65.90; H, 5.81.

**4.1.10. (*S*)-4-Bromo-9a-butyl-8-chloro-6-fluoro-7-hydroxy-1,2,9,9a-tetrahydrofluoren-3-one (1).** To a solution of **14** (10.0 g, 32.4 mmol) in acetic acid (25 mL) and ethanol (50 mL) was added activated charcoal Darco KB-B (2.0 g). The mixture was stirred 1 h, filtered, and rinsed with 1:2 acetic acid/ethanol (35 mL). Imidazole (3.86 g, 56.7 mmol) was added and the solution was cooled to 0 °C. Bromine (1.59 mL, 4.97 g, 31.1 mmol) was added dropwise, maintaining the temperature below 10 °C. The solution was then warmed to 21 °C and water (100 mL) was added slowly to induce crystallization. The solid was collected by filtration and rinsed with 1:1 acetic acid/water. Drying under vacuum at 40 °C gave **1** as an off-white solid (11.06 g, 88%, >99.5% ee). Anal. Calcd for $C_{17}H_{17}BrClFO_2$: C, 52.67; H, 4.42. Found: C, 52.73; H, 4.45.

### 4.2. Measurement of enantiomeric excess

Enantiomer ratios were measured by SFC using isocratic methods with methanol in $CO_2$ at 200 bar and 35 °C with a flow rate of 1.5 mL/min and column dimensions of 250×4.6 mm. For **12**: Chiralpak AD column, 15% methanol, monitoring 320 nm. For **14**: Chiralpak AS column, 27% methanol, monitoring 330 nm. For **1**: Chiralcel OJ column, 25% methanol, monitoring 340 nm.

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