An Efficient Enantioselective Synthesis of the D1 Agonist (5a*R*,11b*S*)-4,5,5a,6,7,11b-Hexahydro-2-propyl-3-thia-5-azacyclopenta[*c*]phenanthrene-9,10-diol (A-86929)

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(5a*R*,11b*S*)-4,5,5a,6,7,11b-Hexahydro-2-propyl-3-thia-5-azacyclopenta[*c*]phenanthrene-9,10-diol (A-86929, **1**), a potent selective dopamine D1 agonist, was synthesized enantioselectively from D-aspartic acid. Key features of the 10-step synthesis are the following: (1) there is no chromatography required; (2) formation of **15** occurs in >99% ee; (3) the electrophilic cyclization to provide the desired *trans* stereochemisry in **18** is achieved with no loss of enantiomeric integrity.

Introduction

We have recently described a new class of dopaminergic compounds, of which (5a*R*,11b*S*)-4,5,5a,6,7,11b-hexahydro-2-propyl-3-thia-5-azacyclopenta[*c*]phenanthrene-9,10-diol, (A-86929, **1**) has been identified as a D1 selective agonist that maintains efficacy upon repeated administration in both rodent and primate models.[1,2] ABT-431, (**2**), the diacetyl prodrug of A-86929, has increased solid state stability and is currently being evaluated in man as therapy for Parkinson's disease. Herein, we report a highly efficient enantioselective synthesis of A-86929.


A-86929, (**1**)   ABT-431, (**2**)
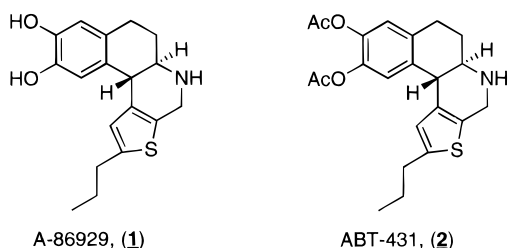
Chemistry

In our initial synthesis of **1**, the racemic 5a and 11b *trans* stereochemistry was set with the Michael addition of 5-allyl-*N*-*tert*-butylthiophenecarboxamide, **3**, into the nitroolefin **4** (Scheme 1). This was followed by conversion of **5** to **6** and the subsequent resolution of **6** to provide enantiomerically pure **1**.[2] We had initially attempted to induce enantioselectivity in this sequence by introducing a chiral auxiliary on the carboxamide of **3**. Unfortunately, this approach was not successful. Reaction conversions were minimal and any **5** which was isolated showed no enhanced enantiomeric excess.

Direction then turned to redesigning the entire synthetic approach to **1**. We decided to employ (*R*)-*N*-(trifluoroacetyl)aspartic anhydride, **7**, as a chiral synthon[3] (Scheme 2). The Friedel−Crafts acylation of veratrole

Scheme 1
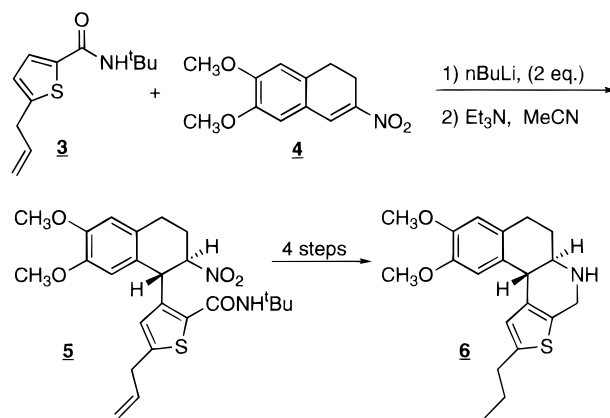
Scheme 2
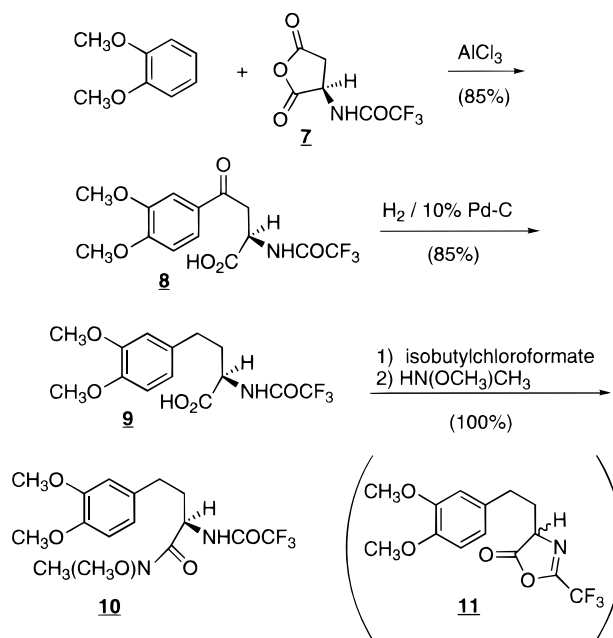
with **7** was performed as previously described by Norlander and co-workers.[4] Hydrogenation of the ketone **8** proceeded well in 1 M HCl/iPA with catalytic palladium to furnish the butanoic acid **9**, which was then converted
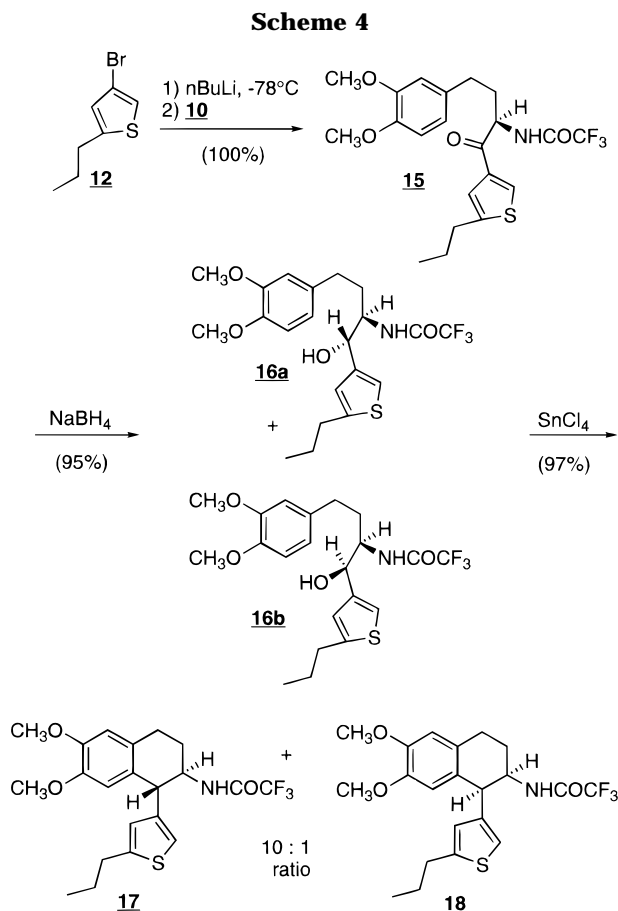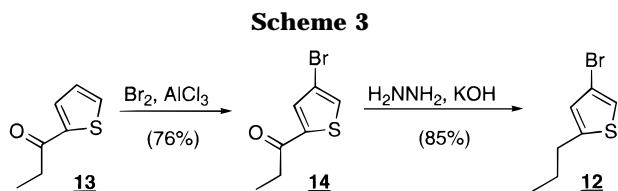

[⊗] Abstract published in *Advance ACS Abstracts,* April 1, 1997.

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Scheme 3

Scheme 4

Table 1. Solvent Effects on the Conversion of 16a and 16b to 17

solvent	reaction time, temp	product ratio (trans:cis), yield, %
CH_2Cl_2	10 min, room temp	4:1, 95%
THF	>3 days, room temp	trans only (20% conversion)
Et_2O	10 h, room temp	3:2, 90%
EtOAc	15 h, room temp	10:1, 97%

Halogen−metal exchange with *n*-butyllithium on **12**, followed by the addition of **10**, afforded the corresponding condensation product **15** in excellent yield (Scheme 4). None of the crude product showed any racemization (ee > 99%),[6] nor was any further addition of the 4-lithio-2-propylthiophene to **15** observed. Reduction of **15** was initially carried out on the crude reaction product, for fear that the α-amino ketone would not maintain its enantiomeric integrity. It has since been determined that **15** can be chromatographed with no detectable racemization taking place.[6]

Reduction of **15** with $NaBH_4$ resulted in a 4:1 ratio of diastereomeric alcohols **16a** and **16b**. The major isomer **16a** could be selectively crystallized; however, this was not necessary as the ratio of **16a** to **16b** had no bearing on the outcome of the following critical cyclization step. We found that upon treatment of pure **16a** or a mixture of **16a** and **16b** with 1 M $SnCl_4/CH_2Cl_2$ with methylene chloride as solvent the product was a 4:1 ratio of the desired *trans* **17** and *cis* **18** with the reaction time being approximately 10 min. In the interest of improving the *trans/cis* product ratio, we performed the conversion at different temperatures ranging from −70 °C to 0 °C in 10° increments. We found that at −10 °C the reaction showed evidence of product formation after 1 h and proceeded at a reasonable pace (monitored by TLC). After a total of 8 h, the reaction was complete and, after workup, showed a 5:1 ratio of **17** to **18**. We saw this as a minimal improvement and decided to look at the effects of different solvents, as shown in Table 1.

When tetrahydrofuran was employed as the solvent, only **17** could be detected, but the reaction times were too prolonged to make this an alternative. Diethyl ether resulted in decreased reaction times, but also decreased *trans* selectivity. Ethyl acetate gave the best results with a reasonable reaction time and significantly improved product ratio. As with **16a** and **16b**, the desired *trans* diastereomer **17** could be selectively crystallized away from **18**. Deprotection of the amide with K_2CO_3 in methanol followed by Pictet−Spengler cyclization then furnished the tetracycle **19** (ee > 99%), as the hydrochloride salt, in 75% overall yield from **12** (Scheme 5).

The demethylation of **19** proceeded smoothly with the agency of BBr_3 to quantitatively furnish **1**. In the formation of **1** it is of interest to note that if performed on the base of **19**, under the same reaction conditions, the product was contaminated with up to 5% of the oxidized byproduct **20**.

to the Weinreb amide **10**, in 55% overall yield from **7**.[5] In our initial studies of the formation of **10**, it was found that short reaction times were crucial to eliminate the formation of an azalactone byproduct, (**11**). The azalactone, which provided a mechanism by which racemization of **10** was facilitated, would constitute up to 15% of the reaction product if the reaction times were 10 min or longer. Fortunately, we discovered that if any of **10** did racemize, it merely required trituration of the crude product with ether; the racemate would then precipitate while the enantiomerically pure amide would remain in solution.[6]

With **10** in hand, we then required 4-bromo-2-propylthiophene (**12**), for the introduction of the D ring (Scheme 3). This was produced via the bromination of 1-(2-thienyl)-1-propanone (**13**),[7] utilizing Br_2 and $AlCl_3$ followed by Wolff−Kishner reduction of ketone **14** in a 65% overall yield.[8]

Conclusion

We have described an efficient unambiguous asymmetric synthesis of A-86929 (**1**), that requires 10 interconversions with no chromatography required and an overall yield of >30%. The key steps in the synthesis are the formation of **15** in >99% ee and the subsequent cyclization to *trans* **18** with no loss of enantiomeric integrity.

(5) Angelastro, M. R.; Peet, Norton, P. P.; Bey, P. *J. Org. Chem.* **1989**, *54*, 3913− 3916.

(6) Enantiomeric excess was determined utilizing an analytical Chiracel OD column purchased from Chiral Technologies Inc., 730 Springdale Dr., Exton, PA. The mobile phase was 9:1 hexanes:iPA, detection = 254 nm, flow = 1mL/min.

(7) Purchased from Aldrich Chemical Company, Inc., Milwaukee, WI 53233.

(8) Alvarez-Insua, A. S.; Conde, S.; Corral, C. *J. Heterocycl. Chem.* **1982**, *19*, 713−716.

Scheme 5
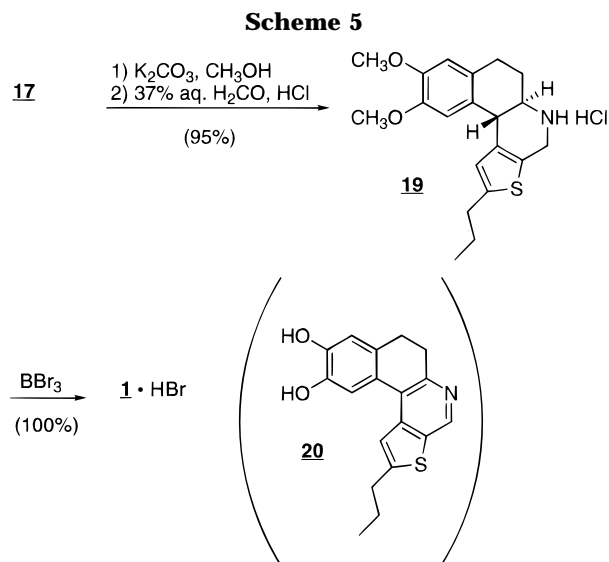
Experimental Section

General. Melting points are uncorrected. All spectral and analytical data were obtained through the Abbott analytical department. All reactions were conducted in oven-dried or flame-dried glassware under a nitrogen atmosphere. Anhydrous solvents were purchased from Aldrich Chemical Co. Analytical TLC was performed by using 2.5 cm × 10 cm plates coated with a 0.25 mm thickness of silica gel containing PF 254 indicator (Analtech). Flash chromatography was performed with silica gel 60 (E. Merck 9285, 230−400 mesh).

(*R*)-(−)-4-(3,4-Dimethoxyphenyl)-2-((trifluoroacetyl)-amino)butanoic Acid (9). A mixture of **8** (237 g, 678.6 mmol), 10% Pd/C (23.7 g), and concentrated HCl (115 mL) in 900 mL of isopropyl alcohol was hydrogenated under 4 atm of hydrogen at rt for 14 h. After filtration of the catalyst over Celite, ether (2 L) was added to the filtrate and the resultant solution was washed with water (4 × 1.5 L). The organic solution was evaporated under reduced pressure to leave an oily residue, which was redissolved in ether (700 mL) and treated with saturated aqueous NaHCO$_3$ until pH 8 was reached. The aqueous solution was separated and washed with ether (2 × 500 mL). After careful acidification to pH 2 by addition of 6 N HCl, the mixture was extracted with ether (2 × 1 L). The organic layers were combined, dried (MgSO$_4$), and concentrated under reduced pressure to give a light brown solid which was recrystallized from hexane/EtOAc. The title compound was obtained as a white crystalline solid (193 g, 85% yield): mp 159−160 °C; ^{1}H NMR (CDCl$_3$) δ 2.05−2.35 (m, 2H), 2.65 (t, 2H, J = 7.5 Hz), 3.70 (s, 3H), 3.80 (s, 3H), 4.60 (br q, 1H, J = 7.5 Hz), 6.70−6.81 (m, 3H), 7.19 (br d, 1H, J = 7.5 Hz). Anal. Calcd for C$_{14}$H$_{16}$F$_3$O$_5$: C, 50.15; H, 4.81; N, 4.18. Found: C, 49.97; H, 4.65; N, 4.15. $[\alpha]_D$ −6.44 (c 1.35, MeOH).

(2*R*)-*N*-Methoxy-*N*-methyl-4-(3,4-dimethoxyphenyl)-2-((trifluoroacetyl)amino)butanamide (10). To a solution of **9** (8 g, 24 mmol) in 65 mL of THF was added *N*-methyl-morpholine, (2.6 mL, 24 mmol), and the solution was cooled to −25 °C and stirred for 30 min. Isobutyl chloroformate (3.1 mL, 24 mmol) was then added, and the solution was stirred for 1.5 min. To this solution was added a solution of *N,O*-dimethylhydroxylamine (prepared by adding *N,O*-dimethyl-hydroxylamine hydrochloride (3.5 g, 36 mmol) to a solution of 24 mL of THF and 1 mL of water, adding K$_2$CO$_3$, (7 g, 216 mmol), stirring for 30 min, and then filtering), and the reaction mixture was stirred for 30 min at −25 °C. The mixture was diluted with ethyl acetate (200 mL), and the organic layer was separated and washed with 50 mL each of water, 1 N NaOH, 1 N HCl, water, and saturated NaCl. The organic layer was then dried over MgSO$_4$ and evaporated to yield a colorless oil. The oil was crystallized from ether/hexanes to yield 7 g of the title compound (77%): mp 70−72 °C; MS m/z 379 (M$^+$ + H), 396 (M$^+$ + NH$_4$); ^{1}H NMR (CDCl$_3$) δ 2.02 (m, 1H), 2.15 (m,

1H), 2.63 (m, 2H), 3.21 (s, 3H), 3.65 (s, 3H), 3.86 (s, 3H), 3.89 (s, 3H), 5.01 (m, 1H), 6.70−6.85 (m, 3H), 7.11 (s, 1H). Anal. Calcd for C$_{16}$H$_{21}$F$_3$N$_2$O$_5$ C, 50.79; H, 5.59; N, 7.40. Found: C, 50.44; H, 5.45; N, 7.34. $[\alpha]_D$ = −8.87° (c = 1.42, CH$_2$Cl$_2$).

1-(4-Bromo-2-thienyl)-1-propanone (14). To a solution of **13** (47.3 g, 338 mmol, Aldrich), in 225 mL of CHCl$_3$ was added AlCl$_3$ (101.3 g, 760 mmol) with stirring. To this mixture was added a solution of bromine (57.5 g, 360 mmol) in 375 mL of CHCl$_3$. The mixture was stirred at rt for 18 h and then poured into 500 mL of ice−water. The organic layer was separated, washed with water (2 × 200 mL), dried over MgSO$_4$, and evaporated to yield 81 g of the crude title compound, which was taken directly to the next step: mp 40−41°C; MS m/z 158 (M$^+$ + H), 236 (M$^+$ + NH$_4$); ^{1}H NMR (CDCl$_3$) δ 1.22 (t, 3H, J = 7.5 Hz), 2.91 (q, 2H, J = 7.5Hz), 7.51 (d, 1H, J = 2Hz), 7.60 (d, 1H, J = 2Hz); IR (KBr) 2960, 1670, 1400, 1220 cm^{-1}.

4-Bromo-2-propylthiophene (12). To a solution of crude **14** (53 g, 242 mmol) in 210 mL of ethylene glycol was added hydrazine monohydrate (30 mL, 617 mmol). The resulting solution was then heated to 160 °C with stirring for 45 min. The solution was cooled to 35 °C, and KOH (42 g, 750 mmol) was added. The mixture was heated to 160 °C and stirred for 1.5 h. The reaction was cooled to rt, and 450 mL of water was added. The mixture was then acidified with concd HCl, and the product was extracted with pentane (3 × 200 mL). The pentane was dried over MgSO$_4$ and evaporated to yield 39.7 g of crude product as a free-flowing oil. The material was purified by flash chromatography on silica gel, eluting with pentane, to afford 33 g, (65% yield) of the title product. Alternatively, the product can be purified by distillation: bp 120−125 °C 7 mmHg; ^{1}H NMR (CDCl$_3$) δ 0.97 (t, 3H, J = 7.5 Hz), 1.69 (sextet, 2H, J = 7.5 Hz), 2.75 (t, 2H, J = 7.5 Hz), 6.70 (d, 1H, J = 2 Hz), 7.00 (d, 1H, J = 2 Hz). Anal. Calcd for C$_7$H$_9$BrS: C, 40.99; H, 4.42. Found: C, 41.04; H, 4.40.

(2*R*)-4-(3,4-Dimethoxyphenyl)-1-(2-propyl-4-thienyl)-2-((trifluoroacetyl)amino)-1-butanone (15). To a solution of **12** (17.4 g, 85 mmol) dissolved in 200 mL of ether and cooled to −78 °C was added 38 mL of 2.5 M nBuLi in hexanes (Aldrich), maintaining the reaction temperature at less than −70 °C. The reaction was stirred at −78 °C for 30 min, and a precooled (−78 °C) solution of **10** (10.7 g, 28.3 mmol) in 50 mL of THF was added at such a rate to maintain the reaction temperature at less than −70 °C. The reaction was quenched with saturated NH$_4$Cl, stirred at rt, and diluted with 300 mL of ethyl acetate. The organic layer was separated and washed with 1 N HCl and saturated NaCl, dried over MgSO$_4$, and evaporated to yield the crude product as an oil (12.5 g, 100%), which was taken directly to the next step: MS m/z 444 (M$^+$ + H), 461 (M$^+$ + NH$_4$); ^{1}H NMR (CDCl$_3$) δ 0.98 (t, 3H, J = 7.5 Hz), 1.68 (m, 2H), 2.04 (m, 1H), 2.30 (m, 1H), 2.63 (dt, 2H, J = 2.4, 7.5 Hz), 2.75 (t, 2H, J = 7.5 Hz), 3.87 (s, 3H), 3.88 (s, 3H), 5.37 (dt, 1H, J = 3, 7.5 Hz), 6.74 (m, 2H), 6.81 (d, 1H, J = 2 Hz), 7.05 (bs, 1H), 7.31 (bd, 1H, J = 9 Hz), 7.72 (d, 1H, J = 2 Hz). Anal. Calcd for C$_{21}$H$_{24}$F$_3$NO$_4$S:C, 56.88; H, 5.46; N, 3.16. Found: C, 56.64; H, 5.45; N, 3.28. $[\alpha]_D$ = −38° (c = 0.75, CHCl$_3$).

(2*R*)-4-(3,4-Dimethoxyphenyl)-1-(2-propyl-4-thienyl)-2-((trifluoroacetyl)amino-1-butanol (16a and 16b). To a solution of **15**, (12.5 g, 28.8 mmol) in 300 mL of absolute ethanol cooled to 0 °C was added 1.4 g (36 mmol) of NaBH$_4$, and the reaction was stirred at rt for 2 h. The reaction was carefully quenched with 1 N HCl and diluted with ethyl acetate. The organic layer was separated and washed with water (2 × 100 mL), and saturated NaCl, dried over MgSO$_4$ and then evaporated to a solid. The solid was triturated with 5:1 hexanes/ethyl acetate to yield pure title product as a 4:1 mixture of *trans:cis* product (12.1 g, 95%: ^{1}H NMR (CDCl$_3$) δ 0.95 (t, $^3/_5$ H, J = 7.5Hz), 0.97 (t, 3H, J = 7.5 Hz), 1.52−1.92 (m, 4$^4/_5$H), 2.42−2.70 (m, 2$^2/_5$H), 2.74 (t, $^2/_5$H, J = 7.5 Hz), 2.75 (t, 2H, J = 7.5 Hz), 3.75 (m, 1H), 3.77 (m, $^1/_5$H), 3.84 (s, 3H), 3.85 (s, 3H), 3.87 (s, $^3/_5$H), 3.88 (s, $^3/_5$H), 4.85 (d, $^1/_5$H, J = 3 Hz), 4.90 (d, 1H, J = 3 Hz), 6.42 (bd, 1H, J = 9 Hz), 6.51 (bd, $^1/_5$H, J = 9 Hz), 6.63 (m, 3$^3/_5$H), 6.70−6.82 (m, 1$^1/_5$H), 6.95 (s, $^1/_5$H), 6.97 (s, 1H); MS m/z 445 (M$^+$ + H), 463 (M$^+$ + NH$_4$).

Anal. Calcd for $C_{21}H_{26}F_3NO_4S$: C, 56.62; H, 5.88; N, 3.14. Found: C, 56.50; H, 5.38; N, 3.14.

***trans*-(1*S*,2*R*)-*N*-(Trifluoroacetyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-1-(2-propyl-4-thienyl)-2-naphthylamine (17)**. To a solution of the alcohols **16a** and **16b** above (7.65 g, 17 mmol) in 200 mL of ethyl acetate cooled to 0 °C was added 17 mL of 1 M SnCl$_4$ in CH$_2$Cl$_2$. The reaction was stirred at rt for 16 h and then quenched with water, and the organic layer was separated, washed with water and saturated NaCl, dried over MgSO$_4$, and evaporated to a solid (6.9 g, 97%). The solid was recrystallized from one part ethyl acetate and five parts hexanes to yield the *trans* title product as a white crystalline solid (5.9 g, 83% yield): mp 157−158 °C; ^{1}H NMR (CDCl$_3$) δ 0.95 (t, 3H, J = 7.5 Hz), 1.66 (m, 2H), 1.88 (m, 1H), 2.10 (m, 1H), 2.72 (t, 2H, J = 7.5 Hz), 2.81 (t, 1H), 2.92 (m, 1H), 3.74 (s, 3H), 3.89 (s, 3H), 4.01 (d, 1H, J = 6 Hz), 4.39 (dt, 1H, J = 3, 7.5 Hz), 6.28 (bd, 1H, J = 7.5 Hz), 6.45 (s, 1H), 6.53 (s, 1H), 6.59 (s, 1H), 6.65 (s, 1H); MS m/z 428 (M$^+$ + H), 445 (M$^+$ + NH$_4$). Anal. Calcd for $C_{21}H_{24}F_3NO_3S$: C, 59.00; H, 5.66; N, 3.28. Found: C, 56.64; H, 5.45; N, 3.28. [α]$_D$ = −18.6° (c 0.05, CH$_2$Cl$_2$).

***trans*-(1*S*,2*R*)-6,7-Dimethoxy-1,2,3,4-tetrahydro-1-(2-propyl-4-thienyl)-2-naphthylamine (17a)**. To a solution of **17** (5.9 g, 13.3 mmol) in 200 mL of 10% aqueous methanol was added 11.8 g of K$_2$CO$_3$ (80 mmol). The resulting suspension was heated at reflux for 2 h, cooled to rt, and diluted with ethyl acetate. The organic layer was washed with water (2 × 100 mL) and saturated NaCl, dried over MgSO$_4$, and evaporated to yield the title compound as an amorphous solid (4.4 g, 100% yield). The compound was taken to the next step without further purification. MS m/z 332 (M$^+$ + H) 349 (M$^+$ + NH$_4$). ^{1}H NMR (CDCl$_3$) δ 0.93 (t, 3H, J = 7.5 Hz), 1.59−1.79 (m, 3H), 2.06 (m, 1H), 2.73 (t, 2H, J = 7.5 Hz), 2.89 (m, 2H), 3.15 (m, 1H), 3.64 (s, 3H), 3.70 (d, 1H, J = 9 Hz), 3.86 (s, 3H), 6.32 (s, 1H), 6.48 (s, 1H), 6.60 (s, 1H), 6.88 (d, 1H, J = 2 Hz). Anal. Calcd for $C_{19}H_{25}NO_2S$: C, 68.85; H, 7.60; N, 4.22. Found: C, 68.63; H, 7.45; N, 4.28.

***trans*-(5a*R*,11b*S*)-9,10-Dimethoxy-4,5,5a,6,7,11b-hexahydro-2-propyl-3-thia-5-azacyclopenta[*c*]phenanthrene Hydrochloride (19)**. To a solution of **17a**, (4.4 g, 13.3 mmol) in 100 mL of absolute ethanol was added 37% formaldehyde in water (10.3 mL, 133 mmol). The reaction was stirred at rt

for 15 min, 3.7 mL of concd HCl was added, and the reaction was heated at reflux for 4 h. The reaction was then cooled, and the suspension was diluted with 200 mL of ether and stirred at rt for 1 h. The mixture was filtered, and the product was dried to yield 4.7 g (95%) of a white crystalline solid: mp 284−286 °C dec; ^{1}H NMR (CDCl$_3$) δ 1.00 (t, 3H, J = 7.5 Hz), 1.69 (m, 3H), 2.39 (m, 1H), 2.62 (m, 1H), 2.79 (t, 2H, J = 7.5 Hz), 2.84−3.09 (m, 2H), 3.18 (m, 1H), 3.83 (s, 3H), 3.88 (s, 3H), 4.30 (d, 1H, J = 10.5 Hz), 4.37 (d, 1H, J = 16.5 Hz), 4.54 (d, 1H, J = 15 Hz), 6.70 (s, 1H), 6.92 (s, 1H), 7.01 (s, 1H); MS m/z 344 (M$^+$ + H), 361 (M$^+$ + NH$_4$). Anal. Calcd for $C_{20}H_{26}$-ClNO$_2$S: C, 63.23; H, 6.90; N, 3.69; Found: C, 62.85; H, 6.83; N, 3.70. [α]$_D$ = −263.14° (c = 3.31, methanol). Base: [α]$_D$ = −343° (c = 0.52, methanol).

***trans*-(5a*R*,11b*S*)-4,5,5a,6,7,11b-Hexahydro-2-propyl-3-thia-5-azacyclopenta[*c*]phenanthrene-9,10-diol Hydrobromide (1)**. A three-neck flask equipped with a mechanical stirrer and a thermometer was charged with a suspension of **19** (19.22 g, 50.6 mmol) in CH$_2$Cl$_2$ (750 mL) and then placed in a dry ice bath. BBr$_3$ (210 mL, 1.0 M solution in CH$_2$Cl$_2$, 210 mmol) was added via syringe over a period of 20 min, resulting in a clear light brown solution. The reaction mixture was stirred at −70 °C for 45 min and then placed in an ice bath and stirred for an additional 2 h. The reaction mixture was recooled to −78 °C and carefully quenched with 180 mL of MeOH. The cooling bath was removed, and the reaction was stirred at rt for 1.5 h. The reaction mixture was concentrated *in vacuo*, and the product was triturated from methanol−CH$_2$Cl$_2$−ether to afford the title product as a tan solid. The product was dried under high vacuum for 16 h to afford 20.1 g (100%) of **1**. The product was >99% pure by HPLC on a reverse phase C-60 Dynamax column using a 1:1 mixture of methanol and 0.1% trifluoroacetic acid as the mobile phase (UV detector at 254 nm): mp 155−162 °C dec; MS m/z 316 (M$^+$ + H); ^{1}H NMR (CDCl$_3$) δ 1.03 (t, 3H, J = 8 Hz), 1.75 (sx, 2H, J = 8 Hz), 1.9−2.0 (m, 1H), 2.28−2.41 (m, 1H), 2.87 (t, 2H, J = 8 Hz), 2.88−3.05 (m, 2H), 3.15−3.27 (m, 1H), 4.02 (d, 1H, J = 11 Hz), 4.46 (s, 2H), 6.67 (s, 1H), 6.90 (s, 1H), 7.02 (s, 1H). Anal. Calcd for $C_{18}H_{22}BrNO_2S\cdot0.7H_2O$: C, 52.87; H, 5.77; N, 3.43. Found: C, 52.87; H, 5.45; N, 3.34. [α]$_D$ = −167° (c 1.03, methanol).