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Divergent asymmetric synthesis of hexahydrobenzophenanthridine dopamine D1 agonists, A-86929, and dihydrexidine

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ABSTRACT

A divergent and scalable asymmetric synthesis of the dopamine D1 agonists, A-86929, and dihydrexidine with high diastereo- and enantioselectivity was accomplished from Weinreb amide **8** derived from inexpensive and easily available L-serine. The synthesis of A-86929 involves only one chromatographic purification.

1. Introduction

Hexahydrobenzophenanthridine compounds, such as dihydrexidine **1** and (−)-(5a*R*,11b*S*)-4,5,-5a,6,7,11b-hexahydro-2-propyl-3-thia-5-azacyclopenta[*c*]phenanthrene-9,10-diol], A-86929 **2a** and its diacetyl prodrug derivative, ABT-431 **2b** (called adrogolide) have shown tremendous promise as full dopamine D1 agonists for the treatment of Parkinson's and other CNS disorders.[1–4] Dihydrexidine **1**, introduced in late 1980s, was the first bioavailable full dopamine D1 receptor agonist and showed approximately a 10-fold selectivity for D1 and D5 over D2. Later, A-86929 **2a** was launched as a full agonist at dopamine D1 receptors and was shown to be over 400 times more selective for dopamine D1 than D2 receptors. There are several methods for the synthesis of these two compounds in the racemic form.[2a,e,5] Since these compounds are found to exhibit a high level of enantiospecificity in their interaction with the D1 receptor, their asymmetric synthesis is an active research area. Ehrlich et al. developed a general chiral-pool approach from expensive *N*-(trifluoroacetyl)-D-aspartic acid anhydride.[6] Tomioka et al. described an elegant and impressive general method for the enantioselective synthesis of both compounds using more than a stoichiometric amount of an expensive chiral ligand.[7] Hajra and Bar reported the first concise, catalytic, and enantioselective synthesis of dihydrexidine and A-86929 using a one-pot asymmetric aziridination and Friedel–Crafts cyclization as the key steps.[8] Recently, we developed the first catalytic enantioselective conjugate addition of arene boronic acids to dihydro-3-nitronaphthalenes and applied them to the formal synthesis of dihydrexidine.[9a] All of the above methods suffer from either using costly reagent/substrate, or from scalability and stereoselectivity problems. Thus the development of an efficient, scalable, and divergent method for the asymmetric synthesis of dihydrexidine **1**, A-86929 **2a,** and related compounds using an inexpensive and easily available substrate/reagent is highly demanding. We have developed a scalable asymmetric synthesis of dihydrexidine in twelve steps from Garner's aldehyde derived from D-serine.[9b] A-86929 could also be synthesized via a similar route from the Garner aldehyde of D-serine. Since hexahydrobenzophenanthridine dopamine D1 agonists have a common aminotetralin unit (upper part) with a variation of the aryl units (lower part), it was more desirable and convenient to synthesize both A-86929 and dihydrexidine and other hexahydrobenzophenanthridines from a common and advanced intermediate with a few simple chemical modifications. Herein we report an efficient and scalable asymmetric synthesis of (+)-dihydrexidine **1** and A-86929 **2a** from homoarylalanine derived from L-serine.

2. Results and discussion

From the literature we found that compounds **1** and **2** could be obtained from aminotetralins **3** and **4**, which in turn could be synthesized from aminoalcohols **5** and **6**, respectively, by a Friedel–Crafts cyclization. These two aminoalcohols can be obtained from aminoaldehyde **7** (Z = H) as well as α-amino Weinreb amide **8** (Z = NMeOMe). The common intermediates **7** and **8** can be easily prepared from the Garner aldehyde **9** of L-serine **10** (Scheme 1).

To start with, Garner aldehyde **9** was synthesized from L-serine **10** in five steps following a well established literature procedure.[10] The enantiomeric purity of **9** was verified by comparing the specific rotation with the literature value.[10] Aldehyde **9** was

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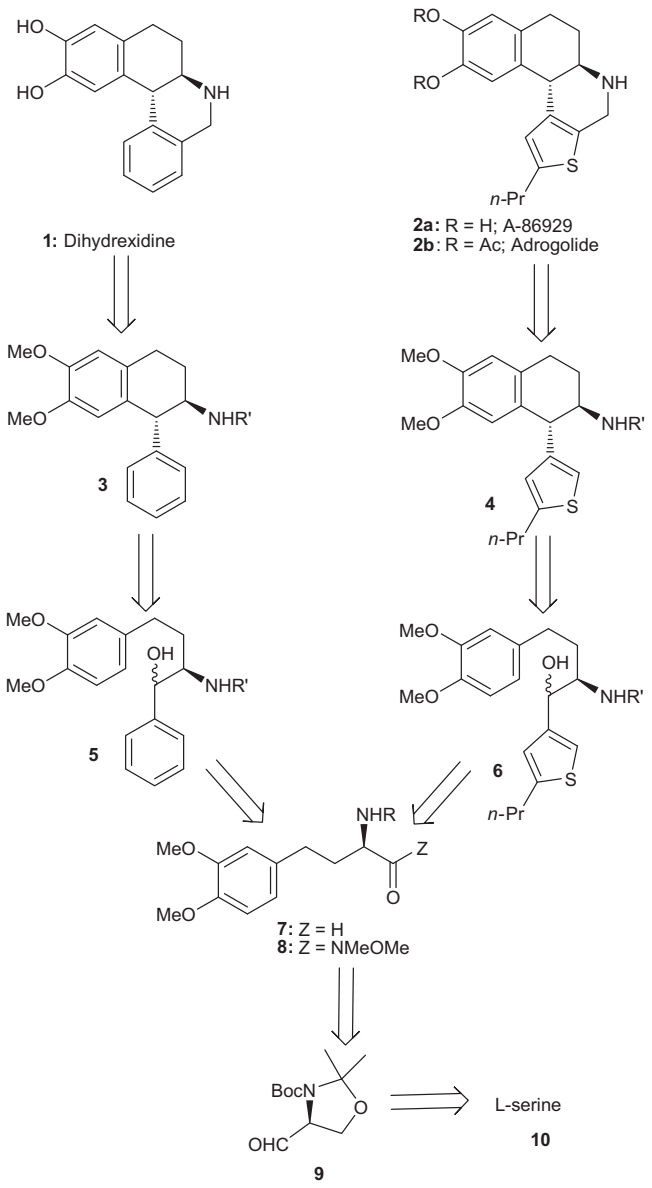


Scheme 1. Retrosynthetic analysis of hexahydrobenzophenanthridine compounds.

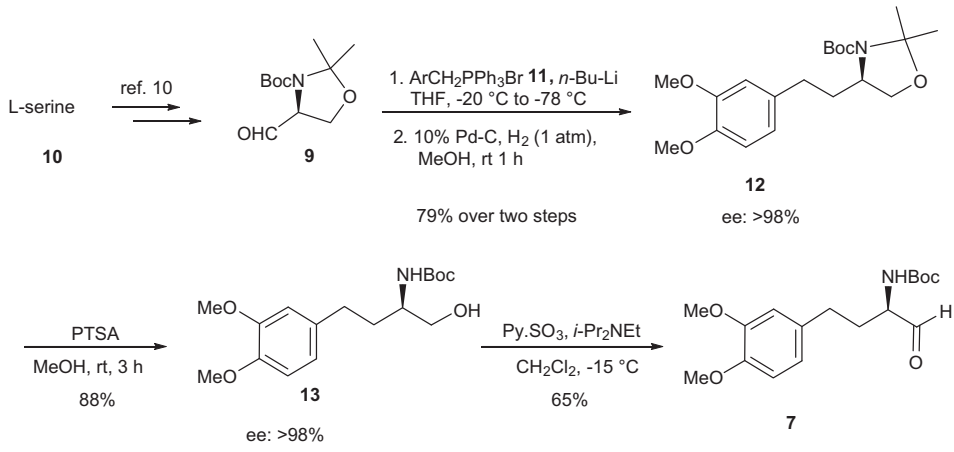
reacted with the ylide generated from (3,4-dimethoxybenzyl)triphenylphosphonium bromide **11** which resulted in the alkene as an *E*/*Z*-mixture (Scheme 2). After removal of the Ph_3PO by-product, it was used directly for the reduction using Pd-C catalyst under an atmospheric pressure of hydrogen (H_2-baloon) and provided the protected amino alcohol **12**. Acetonide deprotection of **12** using PTSA afforded N-protected 2-amino-4-arylbutyl alcohol **13** in high yield. There was no loss of ee over the course of these reactions as the enantiomeric excess of compounds **12** and **13** was found to be very high (ee >98%).[11] Oxidation of alcohol **13** was thought to give aldehyde **7**, which could then be used as an advanced intermediate. However, this was not successful with $(COCl)_2$/DMSO (Swern oxidation), IBX, PDC, or PCC and gave either a poor yield and/or a mixture of uncharacterized compounds. Oxidation with $Py{\cdot}SO_3$ complex and DMSO was found to be very efficient and afforded aldehyde **7** in 65% yield.

Reaction of aldehyde **7** with a variety of metaloarenes (ArM) followed by Friedel–Crafts cyclization and simple chemical modification can afford a large number of hexahydrobenzo–phenanthridine compounds including dihydrexidine and A-86929. In order to accomplish this synthesis, aldehyde **7** was treated with phenyl magnesium bromide at 0 °C and provided N-protected-amino alcohol **5** as a diastereomeric mixture (dr 60:40; Scheme 3). No attempt was made to determine the enantiomeric purity of aldehyde **7**. The preservation of the high enantiomeric excess of both diastereomers **5** (ee >98%) indicated no loss of ee during the oxidation and addition reactions.[11] It is noteworthy that PhLi addition to aldehyde **7** gave a messy reaction mixture under the same reaction conditions. The TFA mediated Friedel–Crafts cyclization of diastereomeric amino alcohol **5** under heating conditions (80 °C) and subsequent treatment of the crude cyclized product with nosyl chloride exclusively afforded *trans*-*N*-nosyl-2-amino-1-phenyltetralin **3** (dr >99:1) while maintaining high enantioselectivity (ee >99%).[11] All of the spectroscopic data and the specific rotation of compound **3** matched well with the literature values.[7b,8a,9b] The synthesis of (+)-dihydrexidine hydrochloride was accomplished from compound **3** as reported in the literature.[9b]

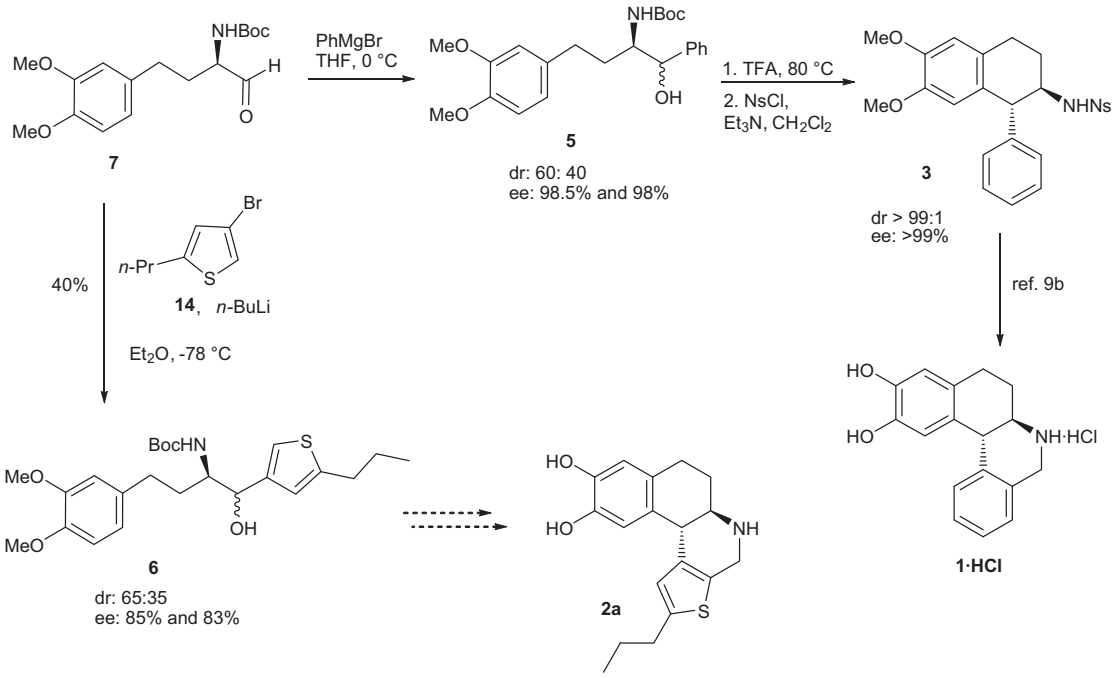
Similarly, a THF solution of aldehyde **7** was reacted with the lithiated thiophene generated from 4-bromo-2-propyl thiophene **14**[6b] but this afforded an intractable mixture of compounds. When the addition of lithiated thiophene to aldehyde **7** was carried out in ether, it gave the desired amino alcohol **6** as a diastereomeric mixture (dr 65:35) in 40% yield, but with a decrease in the ee (85% and 83%).[11] Varying the reaction temperature, solvent, and concentration did not overcome these problems and provided inconsistent results with ee values of 80–95% in low to moderate yields.

The lithiated arene might be more basic than the corresponding Grignard reagent; the former might act as a base for the partial epimerization of aldehyde **5** during the addition reaction. We attempted to prepare the Grignard reagent from 4-bromo-2-propylthiophene using Mg and also *i*-PrMgX, but this was unsuccessful. We therefore looked for a scalable, easy to handle route, where instead of aldehyde **7**, Weinreb amide **8** was used as the advanced intermediate. The TEMPO catalyzed direct oxidation of alcohol **13** to an acid using $NaOCl/NaClO_2$ and $PhI(OAc)_2$ as secondary oxidants was studied.[12] The latter was found to be more efficient for obtaining acid **15**, which was converted into the corresponding Weinreb amide **8** in good yield (Scheme 4). There was complete preservation of the enantiomeric purity during the oxidation and amidation steps, with both acid **15** (ee >98%) and Weinreb amide **8** (ee >98%) showing excellent enantiomeric excess.[11]

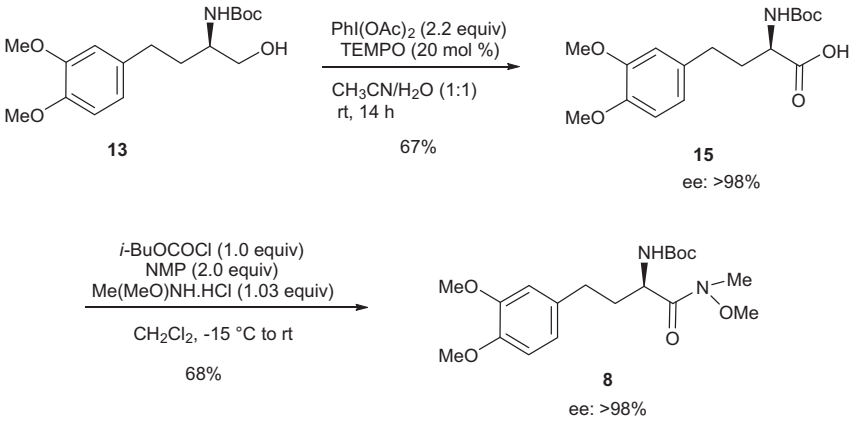
The synthesis of amide **8** was scaled up to 20 g. This proved to be quite stable and could be easily used as a common precursor of the synthesis of many hexahydrobenzophenanthridine compounds. Thus the addition of the lithiated thiophene, generated from 4-bromo-2-propyl thiophene **14**,[6b] to amide **8** was facile and afforded ketone **16** in high yield (81%) without any loss of stereochemical integrity (Scheme 5).[11] Ketone **16** was reduced with $NaBH_4$ and provided the corresponding aminoalcohol **6** as a diastereomeric mixture (dr 75:25) with conservation of the high ee.[11] Unlike the ArLi addition to aldehyde **7** (Scheme 3), it afforded the opposite diastereoselectivity. Compound **6** was subjected to TFA mediated Friedel–Crafts cyclization and underwent smooth cyclization at 50 °C within half an hour to afford 2-amino-1-aryl tetralin **4**. The crude cyclized product **4** was directly used for a Pictet–Spengler cyclization. For this purpose, an aqueous ethanolic solution of compound **4** and formalin was heated with concd HCl for 3 h. Dilution of the ice-cold reaction mixture with ether gave the hydrochloride salt of *O*-methyl A-86929 **17·HCl** as a white solid in 53% yield (over two steps) with excellent diastereo- (dr >99:1) and enantioselectivity (ee >99%).[11] The optical rotation of **17·HCl** $\{[\alpha]_D^{25} = -243$ (*c* 0.55, MeOH)$\}$ was comparable with the lit.[7c] value $\{[\alpha]_D^{25} = -257$ (*c* 0.55, MeOH), $[\alpha]_D^{25} = -263$ (*c* 3.31, MeOH)$\}$ and chiral HPLC analysis showed >99% ee.[11] Finally the demethylation of compound **17** by BBr_3 at −78 °C accomplished the synthesis of A-86929 as its hydrobromide salt **2a·HBr** in 85% yield. The specific



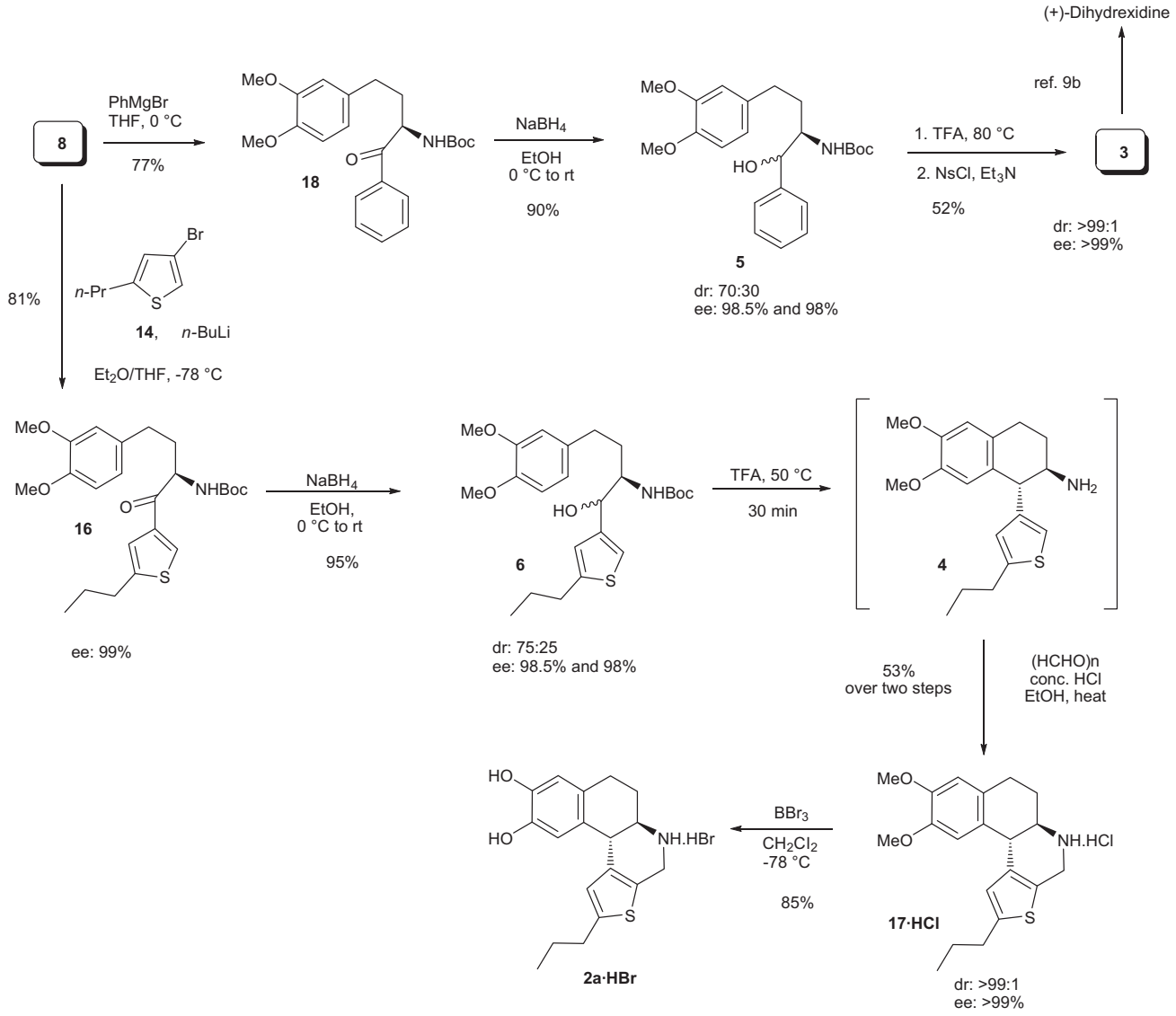
Scheme 2. Synthesis of (*R*)-*N*-Boc-2-amino-4-arylbutyraldehyde **7** from L-serine.



Scheme 3. Formal asymmetric synthesis of dihydrexidine and A-86929 from aldehyde **7**.



Scheme 4. Synthesis of Weinreb amide **8**.



Scheme 5. Divergent asymmetric synthesis of dihydrexidine and A-86929 from Weinreb amide **6**.

rotation of compound **2a·HBr** $\{[\alpha]_D^{23} = -176.2$ (c 1.0, MeOH)$\}$ matched well with the lit.[7c,8b] data $\{[\alpha]_D^{25} = -171$ (c 0.76, MeOH)$\}$. It should be noted that the synthesis of A-86929 from Weinreb amide **8** was achieved using only one column chromatographic purification.

Weinreb amide **8** can be exploited as a common precursor for the synthesis of other hexahydrobenzophenanthridines. As a result, it was further utilized for the synthesis of dihydrexidine. Thus treatment of a THF solution of amide **8** with PhMgBr at 0 °C and subsequent reduction of the product aminoketone **18** with $NaBH_4$ provided aminoalcohol **5** as a diastereomeric mixture in good yield (Scheme 5). It should be noted that the major diastereomer was opposite to the isomer obtained from the addition of PhMgBr to aldehyde **7** (Scheme 3). The TFA mediated Friedel–Crafts cyclization of aminoalcohol **5** followed by reaction with nosyl chloride exclusively afforded *trans*-*N*-nosyl-2-amino-1-phenyltetralin **3** (dr >99:1) in 52% yield with high enantiopurity.[11] Dihydrexidine was synthesized from aminotetralin **3** using our earlier protocol.[9b]

3. Conclusion

In conclusion, we have described a divergent asymmetric protocol for the synthesis of hexahydrobenzophenanthridine compounds from an advanced chiral precursor, derived from L-serine. The synthesis of dopamine D1 agonists, dihydrexidine, and A-86929, started from Weinreb amide **8**, a common intermediate with high diastereo- and enantioselectivity. This method can be scaled up to a few grams and needs minimum column purification. The synthesis of A-86929 from Weinreb amide **8** uses only one column chromatographic purification. Variation in the Wittig reaction and in the addition of metaloarene to the Weinreb amide could provide a variety of hexahydrobenzophenanthridine compounds.

4. Experimental

4.1. General

All reactions were conducted using oven-dried glassware under an argon atmosphere (Ar) or nitrogen (N_2). Commercial grade reagents were used without further purification. Solvents were dried and distilled following the usual protocols. Column chromatography was carried out using silica gel (100–200 mesh). TLC was performed on aluminum-backed plates coated with Silica gel 60 with F_{254} indicator. The ^{1}H NMR spectra were recorded at 400 MHz and ^{13}C NMR spectra were recorded at 100 MHz using $CDCl_3$ and DMSO-d_6. ^{1}H NMR chemical shifts are expressed in parts per

million (δ) relative to $CDCl_3$ (δ = 7.26) and DMSO-d_6 (δ = 2.49); ^{13}C NMR chemical shifts are expressed in parts per million (δ) relative to the $CDCl_3$ resonance (δ = 77.0), DMSO-d_6 (δ = 39.7), and MeOH-d_4 (δ = 49.0). High resolution mass spectra (HRMS) were obtained under positive electron spray ionization (m/z values are given). Chiral HPLC analyses were carried out comparing with the corresponding racemic compound by Chiralpak AD-H column (4.6 × 250 mm), Chiralpak-IC column (4.6 × 250 mm), and Lux Amylose-2 column (4.6 × 250 mm). Specific rotation values were measured on a polarimeter.

4.1.1. (*R*)-*tert*-Butyl 4-(3,4-dimethoxyphenethyl)-2,2-dimethyloxazolidine-3-carboxylate 12

To a suspension of (3,4-dimethoxybenzyl)triphenylphosphonium bromide (25.5 g, 51.78 mmol) in anhydrous THF (100 mL) was added *n*-butyllithium (2.35 M, 26.8 mL, 45.5 mmol) at −20 °C under an argon atmosphere. The reaction mixture was stirred at −20 °C for 20 min and cooled to −78 °C. A solution of Garner aldehyde **7** (9.5 g, 41.43 mmol) in anhydrous THF (80 mL) was added dropwise to the reaction mixture. The resulting mass was stirred at −78 °C for 45 min and then slowly raised to −10 °C. The reaction was quenched with a saturated aqueous ammonium chloride solution (250 mL) and extracted with ethyl acetate (3 × 200 mL). The combined organic layers were washed with water (200 mL), saturated brine (250 mL), and dried over anhydrous sodium sulfate. The solvent was removed under vacuum and most of the triphenylphosphine oxide was removed by precipitation on stirring with 50% ether in hexanes. Column chromatography of the crude product over silica gel gave an *E*/*Z* mixture of the olefin (13.2 g) as a colorless sticky oil. The oily compound was dissolved in methanol (100 mL) and thoroughly degassed using nitrogen. The 10% Pd-C catalyst (0.25 g, 1.8 mmol) was then added and hydrogenated using a hydrogen-balloon at rt for 1 h. The reaction mass was filtered over a Celite bed and washed with methanol (50 mL). The solvent was removed under vacuum and the crude product was purified by column chromatography to afford pure compound **12** (11.9 g, 79% over two steps) as a colorless sticky oil. ^1H NMR ($CDCl_3$, 400 MHz): δ 6.78–6.55 (m, 3H), 3.91 (m, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.75 (m, 1H), 2.53 (m, 2H), 2.11–1.90 (m. 2H), 1.57 (s, 3H), 1.52 (s, 3H), 1.52 (s, 3H), 1.45 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.0, 148.9, 147.2, 134.1, 120.0, 111.7, 111.4, 93.1, 79.3, 66.8, 66.8, 57.4, 55.9, 55.8, 35.5, 32.3, 28.3, 27.5, 24.4. LC–MS (ESI): 365.8 $[M+H]^+$, 387.8 $[M+Na]^+$. HPLC analysis: CHIRALCEL OD-H (4.6 × 250 mm) 5μ, *n*-hexane/*i*-PrOH/diethyl amine: 90:10:0.1, 1.0 mL/min, 280 nm, t_r (major) 5.54, t_r (minor) 5.21; ee >98%. $[\alpha]_D^{25} = -37.7$ (*c* 0.51, $CHCl_3$). HRMS (ESI): Calcd for $C_{20}H_{31}NO_5Na$, 388.2100 m/z $[M+Na]^+$, found 388.2100.

4.1.2. (*R*)-*tert*-Butyl (4-(3,4-dimethoxyphenyl)-1-hydroxybutan-2-yl)carbamate 13

A solution of compound **12** (7.45 g, 20.4 mmol) and PTSA (0.250 g, 1.8 mmol) in methanol (105 mL) was stirred at room temperature for 3 h and the solvents then removed under vacuum. The residue was diluted with ethyl acetate (250 mL) and washed successively with a saturated aqueous sodium bicarbonate solution (200 mL), water (200 mL), and brine (200 mL). The organic layer was dried over anhydrous sodium sulfate and removed under vacuum to give the crude product, which was purified by column chromatography over silica gel to provide compound **13** (5.8 g, 88%) as a white solid. Mp 70–72 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ 6.79–6.77 (m, 1H), 6.72–6.70 (m, 2H), 4.63 (br s, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.66 (m, 2H), 3.57–3.55 (m, 1H), 2.66–2.60 (m, 2H), 2.2 (br s,1H), 1.82–1.73 (m, 2H), 1.45 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.4, 148.7, 147.1, 134.1, 120.0, 111.6, 111.2, 79.5, 65.6, 55.8, 55.7, 52.2, 33.4, 31.8, 28.3(3C). LC–MS (ESI): 326.4 $[M+H]^+$, 348.6 $[M+Na]^+$. HPLC analysis: CHIRALPAK AD-H (4.6 × 250 mm) 5μ, *n*-hexane/*i*-PrOH 90:10, 1.0 mL/min, 210 nm, t_r (major) 11.00, t_r (minor) 12.41; ee >98%. $[\alpha]_D^{25} = +9.3$ (*c* 0.77, $CHCl_3$). HRMS (ESI): Calcd for $C_{17}H_{27}NO_5Na$, 348.1787 m/z $[M+Na]^+$, found 348.1787.

4.1.3. (*R*)-*tert*-Butyl (4-(3,4-dimethoxyphenyl)-1-oxobutan-2-yl)carbamate 7

To a stirred solution of compound **13** (1.0 g, 3.07 mmol) in anhydrous dichloromethane (9.0 mL) was added anhydrous diisopropylethylamine (1.6 mL, 9.2 mmol) at −15 °C under a nitrogen atmosphere. A solution of pyridine–sulfur trioxide complex ($Py{\cdot}SO_3$; 1.46 g, 9.23 mmol) in anhydrous DMSO (9 mL) was added to the above solution in one portion. The reaction mixture was stirred at the same temperature for 30 min and then slowly poured into ice cold brine (200 mL), and extracted with dichloromethane (3 × 50 mL). The combined organic extract was washed with a 10% aqueous citric acid solution (50 mL), brine (50 mL), dried over anhydrous sodium sulfate, filtered, concentrated, and purified by column chromatography to afford compound **7** (0.65 g, 65%). ^1H NMR ($CDCl_3$, 400 MHz): δ 9.54 (s, 1H), 6.79–6.78 (m, 1H), 6.72–6.70 (m, 2H), 5.05 (br s, 1H), 4.24 (br s, 1H), 3.86 (s, 3H), 3.85(s, 3H), 2.65 (t, *J* = 7.8 Hz, 2H), 2.20–2.18 (m, 1H), 1.89–1.82 (m, 1H), 1.45 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 199.6, 155.5, 148.9, 147.5, 133.1, 120.3, 120.1, 111.7, 111.4, 80.1, 59.4, 55.8, 55.8, 31.0, 30.9, 28.2.

4.1.4. (*R*)-2-((*tert*-Butoxycarbonyl)amino)-4-(3,4-dimethoxyphenyl)butanoic acid 15

To a stirred solution of compound **13** (2.4 g, 7.3 mmol) in aqueous acetonitrile (1:1, 17 mL) were successively added diacetoxyiodobenzene (5.2 g, 16.1 mmol) and 2,2,6,6-tetramethyl-1-piperidinyl free radical (TEMPO; 0.23 g, 1.5 mmol) at rt. The reaction mixture was then stirred overnight at ambient temperature. After removal of the solvent under reduced pressure, the reaction mass was diluted with sodium hydroxide solution (4 M, 9 mL) and washed with diethyl ether (2 × 50 mL). The aqueous layer was acidified to pH ~4 by the dropwise addition of hydrochloric acid solution (4 M) at an ice bath temperature. The compound was extracted into ethyl acetate (2 × 50 mL), and the combined organic layers washed with water (50 mL), brine (100 mL), dried over anhydrous sodium sulfate. The solvent was removed in order to obtain the crude product, which was purified by column chromatography over silica gel to give acid **15** (1.7 g, 67%). ^1H NMR (DMSO-d_6, 400 MHz): δ 12.41 (s, 1H; CO_2H), 7.18 (d, *J* = 8.0 Hz, 1H; N*H*), 6.84 (d, *J* = 8.2 Hz, 1H), 6.78 (s, 1H), 6.68 (d, *J* = 8.2 Hz, 1H), 3.84–3.81 (m, 1H), 3.72 (s, 3H), 3.70 (s, 3H), 3.28–3.26 (m, 1H), 2.57–2.54 (m, 1H), 1.91–1.79 (m, 2H), 1.40 (s, 9H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 174.2, 155.6, 148.5, 146.9, 133.5, 120.0, 112.3, 111.8, 77.9, 55.4, 55.2, 52.7, 32.8, 31.1, 28.1(3C). LC–MS (ESI): 340 $[M+H]^+$, 357.2 $[M+NH_4]^+$. HPLC analysis: CHIRALPAK-IC (4.6 × 250 mm) 5μ, *n*-hexane/EtOH/diethylamine: 70:30:0.1, 1.0 mL/min, 280 nm, t_r (major) 7.97, t_r (minor) 10.40, ee >98%. $[\alpha]_D^{25} = +4.1$ (*c* 0.51, MeOH). HRMS (ESI): Calcd for $C_{17}H_{25}NO_6$-Na, 362.1580 m/z $[M+Na]^+$, found 362.1580.

4.1.5. (*R*)-*tert*-Butyl (4-(3,4-dimethoxyphenyl)-1-(methoxy(methyl)amino)-1-oxobutan-2-yl)carbamate 8

To the solution of compound **15** (3.3 g, 9.7 mmol) in anhydrous dichloromethane (35 mL) was added *N*-methylmorpholine (2.1 mL, 19.5 mmol). The reaction mixture was cooled to −15 °C and isobutylchloroformate (1.26 mL, 9.7 mmol) was added and stirred. After 15 min, *N*,*O*-dimethylhydroxylamine hydrochloride (0.98 g, 10.02 mmol) was added at this temperature (−15 °C). The mixture was then stirred at −15 °C for an additional 1 h and then allowed to warm to rt and stirred for 1 h. The reaction mixture was poured into ice cold water (40 mL) and extracted with dichloromethane (2 × 50 mL). The combined organic layer was washed with

water, brine, and dried over anhydrous sodium sulfate. The solvent was removed under vacuum and the crude product was purified by column chromatography over silica gel to provide the title compound **8** (2.5 g, 68%) as a colorless sticky mass. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.79–6.73 (m, 3H), 5.19 (m,1H), 4.68 (br s, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.62 (s, 3H), 3.16 (s, 3H), 2.68–2.65 (m, 1H), 2.62–2.57 (m, 1H), 1.99–1.97 (m, 1H), 1.82–1.78 (m, 1H), 1.44 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.1, 155.5, 148.7, 147.2, 133.7, 120.3, 111.9, 111.2, 79.5, 61.4, 55.9, 55.8, 49.9, 34.6, 31.2, 28.3 (3C). LC–MS (ESI): 383.2 $[M+H]^+$. HPLC analysis: CHIRALPAK-IA (4.6 × 250 mm) 5μ, 100% EtOH, 0.5 mL/min, 210 nm, t_r (major) 10.12, t_r (minor) 8.05, ee >98%. $[\alpha]_D^{25} = +11$ (*c* 0.51, MeOH). HRMS (ESI): Calcd for $C_{19}H_{30}N2O_6Na$, 405.2002 *m*/*z* $[M+Na]^+$, found 405.2002.

4.1.6. (*R*)-*tert*-Butyl (4-(3,4-dimethoxyphenyl)-1-oxo-1-(5-propylthiophen-3-yl)butan-2-yl)carbamate 16

To a solution of compound **14** (1.9 g, 9.3 mmol) in anhydrous diethyl ether (16 mL) was added dropwise *n*-butyl lithium (2.03 M in hexanes; 3.9 mL, 7.9 mmol) at −78 °C under nitrogen and stirred for 40 min. A pre-cooled (−78 °C) solution of Weinreb amide **8** (1.03 g, 2.7 mmol) in anhydrous THF (6.0 mL) was then added dropwise. The reaction mass was stirred at −78 °C for 1 h and then carefully quenched with a saturated aqueous ammonium chloride solution (20 mL), after which it was allowed to return to rt and diluted with ethyl acetate (100 mL). The layers were separated, and the organic layer was washed with water, brine, and dried over anhydrous sodium sulfate. The solvent was removed under vacuum and the crude product was purified by column chromatography over silica gel to afford ketone **16** (1.04 g, 81%) as a colorless sticky mass. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.74 (s, 1H), 7.06 (s, 1H), 6.78 (d, *J* = 8.0 Hz, 1H), 6.73 (d, *J* = 8.0 Hz, 1H), 6.71 (s, 1H), 5.38 (d, *J* = 8.7 Hz, 1H), 5.04 (m, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 2.72 (t, *J* = 7.3 Hz, 2H), 2.64 (t, *J* = 7.3 Hz, 2H), 2.15–2.11 (m, 1H), 1.88–1.82 (m, 1H), 1.68–1.61 (m, 2H), 1.44 (s, 9H), 0.95 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 193.3, 155.5, 148.9, 147.4, 147.0, 139.1, 133.5, 131.5, 123.6, 120.4, 112.0, 111.3, 79.7, 55.9, 55.8, 55.2, 35.7, 31.8, 31.1, 28.3 (3C), 24.5, 13.5. LC–MS (ESI): 448.2 $[M+H]^+$, 465.2 $[M+NH_4]^+$. HPLC analysis: CHIRALPAK-IA (4.6 × 250 mm) 5μ, 100% EtOH, 0.5 mL/min, 210 nm, t_r (major) 10.37, t_r (minor) 9.38, ee >98%. $[\alpha]_D^{25} = -28.5$ (*c* 0.39, CH_2Cl_2). HRMS (ESI): Calcd for $C_{24}H_{33}NO_5SNa$, 470.1977 *m*/*z* $[M+Na]^+$, found 470.1977.

4.1.7. *tert*-Butyl [(1*R*,2*R*)- and (1*S*,2*R*)-4-(3,4-dimethoxyphenyl)-1-hydroxy-1-(5-propylthiophen-3-yl)butan-2-yl]carbamate 6

To a solution of compound **16** (0.720 g, 1.6 mmol) in absolute ethanol (17 mL) was added sodium borohydride (0.077 g, 2.0 mmol) in portions at 0 °C under nitrogen and then allowed to stir at ambient temperature for 1 h. The reaction mass was quenched with a saturated aqueous ammonium chloride solution (10 mL). The product was extracted into ethyl acetate (2 × 50 mL), and the combined organic layer washed with water, brine, dried over anhydrous sodium sulfate and the solvent removed under vacuum to afford alcohol **6** (0.65 g, 90%) as a diastereomeric mixture (dr 75:25). The crude product **6** was used as such in the next step without any purification. Mp 76–80 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (major isomer) 6.9 (s, 1H), 6.75 (d, *J* = 8.0 Hz, 1H), 6.67 (m, 2H), 6.63 (s, 1H), 4.81 [s, 1H; ArC*H*OH; minor isomer 4.59 (d, *J* = 8.0 Hz)], 4.66 (br s, 1H), 3.83 (s, 6H), 3.84 (m, 1H), 2.80–2.40 (m, 4H), 1.75–1.51 (m, 4H), 1.45 (s, 9H), 0.94 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 193.3, 155.5, 148.9, 147.4, 147, 139.1, 133.5, 131.5, 123.6, 120.4, 112.0, 111.3, 79.7, 55.9, 55.8, 55.2, 35.7, 31.8, 31.1, 28.3, 24.5, 13.5. LC–MS (ESI): 450.0 $[M+H]^+$. HPLC analysis: CHIRALPAK-IA (4.6 × 250 mm) 5μ, hexane/IPA: 90:10, 1.0 mL/min, 230 nm, major diastereomer t_r (major) 12.75, t_r (minor) 11.21, ee 98.5%; minor diastereomer t_r (major) 20.84, t_r (minor) 9.65, ee 98%. HRMS (ESI): Calcd for $C_{24}H_{35}NO_5SNa$, 472.2134 *m*/*z* $[M+Na]^+$, found 472.2134.c

4.1.8. (5a*R*,11b*S*)-9,10-Dimethoxy-2-propyl-4,5,5a,6,7,11b-hexahydrobenzo[f]thieno[2,3-c]quinoline hydrochloride 17·HCl

A solution of compound **6** (0.30 g, 0.67 mmol) in anhydrous trifluoroacetic acid (1.5 mL) was heated at 50 °C on a pre-heated oil bath for 30 min. The residue was neutralized with a saturated aqueous sodium bicarbonate solution under ice-cold conditions. The product was extracted into ethyl acetate (3 × 30 mL). The combined organic layer was washed with water, brine, dried over anhydrous sodium sulfate, and the solvents were removed under vacuum to afford aminotetralin **4** (0.23 g, 100%) which was used immediately in the next step without any purification.

To the solution of crude compound **4** (0.23 g, 0.67 mmol) in absolute ethanol (5.0 mL) was added 37% formalin (0.52 mL). The reaction mixture was stirred at rt for 15 min. after which concd HCl (0.19 mL) was added and then heated at 50 °C for 30 min. The reaction mixture was cooled to rt, diluted with diethyl ether (10 mL) and stirred for 45 min. The suspended solution was filtered and the solid product was washed with diethyl ether (5 mL) to provide diastereo- and enatiomerically pure *O*-methyl A-86929 as a hydrochloride salt **17·HCl** (0.135 g, 53%) as a white solid. Mp 270–272 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.70 (br s, 1H), 10.20 (br s, 1H), 6.98 (s, 1H), 6.84 (s, 1H), 6.68 (s, 1H), 4.54 (d, *J* = 15.7 Hz, 1H), 4.34 (d, *J* = 15.7 Hz, 1H), 4.29 (d, *J* = 10.8 Hz, 1H), 3.86 (s, 3H), 3.82 (s, 3H), 3.15 (m, 1H), 2.99 (m, 1H), 2.90–2.77 (m, 1H), 2.78 (t, *J* = 7.2 Hz, 2H), 2.61 (m, 1H), 2.37 (m, 1H), 1.70 (m, 2H), 0.98 (t, *J* = 7.2 Hz, 3H); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.82 (br s, 2H), 7.12 (s, 1H), 6.94 (s, 1H), 6.87 (s, 1H), 4.43 (d, *J* = 15.6 Hz, 1H), 4.35 (d, *J* = 15.6 Hz, 1H), 4.06 (d, *J* = 10.6 Hz, 1H), 3.74 (s, 3H), 3.69 (s, 3H), 3.17 (m, 1H), 2.90 (m, 2H), 2.83 (t, *J* = 7.0 Hz, 2H), 2.28 (m, 1H), 1.90 (m, 1H), 1.64 (m, 2H), 0.93 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 147.9, 147.2, 145.4, 134.5, 129.0, 127.6, 125.0, 123.7, 111.8, 109.9, 57.6, 56.0, 55.9, 42.7, 39.7, 32.1, 26.8, 24.9, 24.7, 13.5. LC–MS (ESI): 344.2 $[M+H]^+$. HPLC analysis: Lux amylose-2 (4.6 × 250 mm) 5μ, hexane/EtOH/diethyl amine 80:20:0.1, 1.0 mL/min, 285 nm, t_r (major) 7.26, t_r (minor) 16.4, ee >99%. $[\alpha]_D^{25} = -243.3$ (*c* 0.55, MeOH) {lit.[7c] $[\alpha]_D^{25} = -257$ (*c* 0.55, MeOH)}.

4.1.9. (5a*R*,11b*S*)-2-Propyl-4,5,5a,6,7,11b-hexahydrobenzo[*f*]thieno[2,3-*c*]quinoline-9,10-diol hydrobromide 2a·HBr (A-86929·HBr)

To compound **17·HCl** (0.084 g, 0.24 mmol) in dry DCM (1.6 ml) was added BBr_3 (0.9 ml, 1.0 M solution in CH_2Cl_2) at −78 °C. The reaction mixture was stirred at −78 °C for 1 h and then placed in an ice bath and stirred for 2 h. The reaction mixture was further cooled to −78 °C and quenched with 1.0 mL of MeOH. The cooling bath was removed and the mixture was stirred for 2 h at rt, after which it was concentrated under reduced pressure and the sticky mass was triturated with ether to give a pure product as a light brown solid. (0.07 g, 85%). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.44 (br s, 1H), 9.25 (br s, 1H), 8.76 (s, 1H), 8.75 (s, 1H), 6.99 (s, 1H), 6.79 (s, 1H), 6.59 (s, 1H), 4.45 (d, *J* = 16.0 Hz, 1H), 4.40 (m, 1H), 3.92 (d, *J* = 10.2 Hz, 1H), 3.16 (m, 1H), 2.81 (t, *J* = 7.6, 2H), 2.88–2.66 (m, 2H), 2.18 (m, 1H), 1.81 (m, 1H), 1.66 (m, 2H), 0.96 (t, *J* = 7.3 Hz, 3H). ^{1}H NMR (d_4-MeOH, 400 MHz): δ 6.99 (s, 1H), 6.87 (s, 1H), 6.65 (s, 1H), 4.45 (AA′ t, *J* = 17.2 Hz, 2H), 4.00 (d, *J* = 10.9 Hz, 1H), 3.19 (m, 1H), 2.99–2.86 (m, 1H), 2.84 (t, *J* = 7.5 Hz, 2H), 2.80 (m, 1H), 2.37–2.28 (m, 1H), 1.97–1.88 (m, 1H), 1.71 (m, 2H), 1.00 (t, *J* = 7.2 Hz, 3H). ^{1}H NMR (MeOH-d_4, 100 MHz): δ 147.1, 145.3, 144.6, 134.6, 129.1, 128.7, 126.7, 125.7, 116.5, 113.5, 58.7, 44.3, 40.7, 33.0, 26.5, 26.2, 26.0, 13.8. LC–MS (ESI): 316.2 $[M+H]^+$. $[\alpha]_D^{25} = -176.2$ (*c* 1.0, MeOH) {lit.[7c] $[\alpha]_D^{25} = -171$ (*c* 0.76, MeOH)}.

4.1.10. (*R*)-*tert*-Butyl (4-(3,4-dimethoxyphenyl)-1-oxo-1-phenylbutan-2-yl)carbamate 18

To a solution of Weinreb amide **8** (0.30 g, 0.78 mmol, 1.0 equiv) in anhydrous THF (2.4 mL) at 0–5 °C was added phenylmagnesium bromide (1 M in THF; 1.6 ml, 2.1 equiv, 1.6 mmol) over 10 min. The mixture was then allowed to return to ambient temperature over 90 min and then brought to 0–5 °C followed by the careful addition of aqueous ammonium chloride solution. It was then extracted by ethyl acetate (3 × 50 mL). The combined organic extract was washed once with brine and evaporated under reduced pressure. The crude mass was purified by flash chromatography using ethyl acetate in hexane to afford ketone **18** (0.21 g, 67%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, J = 7.6 Hz, 2H), 7.50 (m, 1H), 7.37 (m, 2H), 6.73 (d, J = 8.1 Hz, 1H), 6.67–6.64 (m, 2H), 5.54 (d, J = 7.8 Hz, 1H), 5.29 (m,1H), 3.79 (s, 3H), 3.77 (s, 3H), 2.66–2.59 (m, 2H), 2.13–2.1 (m, 1H), 1.83–1.78 (m, 1H), 1.42 (s, 9H). ^{13}C NMR (100 MHz, CDCl3): δ 199.0, 155.4, 148.7, 147.2, 134.4, 133.4, 133.2, 128.5(2C), 128.3(2C), 120.3, 111.8, 111.2, 79.5, 55.7, 55.6, 54.2, 35.2, 30.8, 28.1(3C). $[\alpha]_D^{25} = -24.7$ (c 2.95, $CHCl_3$). LC–MS (ESI): 400.0 $[M+H]^+$, 417 $[M+NH_4]^+$. HRMS (ESI): Calcd for $C_{23}H_{29}NO_5Na$, 422.1943 m/z $[M+Na]^+$, found 422.1943.

4.1.11. *tert*-Butyl [(1*R*,2*R*)- and (1*S*,2*R*)-4-(3,4-dimethoxyphenyl) -1-hydroxy-1-phenylbutan-2-yl]carbamate 5[9b]

To a solution of ketone **18** (0.20 g, 0.5 mmol) in absolute ethanol (5 mL) was added sodium borohydride (0.024 g, 1.8 mmol) in portions at 0 °C under nitrogen and then allowed to stir at ambient temperature for 1 h. The reaction mass was quenched with a saturated aqueous ammonium chloride solution (5 mL). The product was extracted into ethyl acetate (2 × 30 mL), and the combined organic layer washed with water, brine, dried over anhydrous sodium sulfate, and the solvent was removed under vacuum to afford alcohol **5** (0.18 g, 91%) as a diastereomeric mixture (dr 70:30). The crude product **5** was used in the next step without any purification. ^{1}H NMR ($CDCl_3$, 400 MHz): major isomer: δ 7.33–7.25 (m, 5H C_6H_5), 6.76 (d, J = 8.0 Hz, 1H), 6.66 (d, J = 8.0 Hz, 1H), 6.64 (s, 1H), 4.67 (d, J = 4.3 Hz, 1H, PhC*H*OH) [minor isomer 4.74 (d, J = 8.1 Hz)], 4.66 (s, 1H, N*H*), 3.83 (s, 6H), 3.73 (m, 1H), 2.23 (br s, 1H), 2.66 (m, 1H), 2.55 (m, 1H), 1.85 (m, 1H), 1.71 (m, 1H), 1.38 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.4, 148.7, 147.0, 141.6, 134.1, 128.1, 127.5, 126.2, 120.1, 111.6, 111.1, 79.4, 76.1, 56.1, 55.8, 55.6, 33.4, 31.9, 28.2. HPLC analysis: CHIRALPAK-IA (4.6 × 250 mm) 5μ, *n*-hexane/*i*-PrOH: 80:20, 1.0 mL/min, 220 nm, major diastereomer t_r (major) 7.37, t_r (minor) 6.86, ee 98.5%; minor diastereomer t_r (major) 11.21, t_r (minor) 8.49, ee 98%. LC–MS (ESI): 402.0 $[M+H]^+$.

4.1.12. *N*-((1*R*,2*R*)-6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydronaphthalen-2-yl)-4-nitrobenzenesulfonamide 3

Compound **5** (0.156 g, 0.389 mmol) was heated with trifluoroacetic acid (1.5 mL) at 80 °C on a preheated oil bath for 5 h, concentrated under reduced pressure, and neutralized with a saturated aqueous solution of sodium bicarbonate. The product was extracted into ethyl acetate (3 × 20 mL). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was dissolved in anhydrous dichloromethane (8 mL) and cooled to 0 °C under nitrogen. Anhydrous triethylamine (0.16 ml, 1.16 mmol) and nosyl chloride (0.13 g, 0.58 mmol) were then added at 0 °C. The reaction mixture was then stirred at rt for 2 h, quenched with a saturated aqueous sodium bicarbonate solution (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). Combined organic layer was washed with brine, dried over sodium sulfate, and the solvent was evaporated. Column chromatographic purification followed by crystallization from MeOH at −5 °C afforded exclusively *trans*-*N*-nosyl-2-amino-1-phenyltetralin **3** (0.095 g, 52%) as a yellow solid with excellent enantioselectivity (ee >99%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.15 (d, J = 8.8 Hz, 2H), 7.73 (d, J = 8.8 Hz, 2H), 7.15–7.09 (m, 3H), 6.83 (d, J = 6.64 Hz, 2H), 6.59 (s, 1H), 6.07 (s, 1H), 4.74 (d, J = 7.8 Hz, 1H), 3.84 (s, 3H), 3.81 (d, J = 7.2 Hz, 1H), 3.63 (m, 1H), 3.56 (s, 3H), 2.96–2.87 (m, 1H), 2.83- 2.76 (m, 1H), 2.25–2.21 (m, 1H), 1.78–1.73 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): 149.6, 148.0, 147.5, 146.0, 142.9, 128.8, 128.5, 127.9, 127.6, 127.4, 127.0, 124.1, 112.8, 110.8, 57.1, 55.8, 55.7, 51.5, 27.7, 26.1. LC–MS (ESI) m/z: 467.2 $[M+H]^+$. Chiral HPLC analysis: CHIRALPAK AD-H (4.6 × 250 mm) 5μ, *n*-hexane/*i*-PrOH 90:10, 1.0 mL/min. 220 nm, t_r (major) 25.2, t_r (minor) 33.1 ee >99%. $[\alpha]_D^{25} = -64.4$ (c 0.96, $CHCl_3$) {lit.[9b] $[\alpha]_D^{25} = -64.2$ (c 1.00, $CHCl_3$); lit.[8a] $[\alpha]_D^{25} = -51.2$ (c 1.00, $CHCl_3$)}.

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