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Note

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Diastereoselective Pictet-Spengler Based Synthesis of a Chiral Tetrahydroisoquinoline D1 Potentiator

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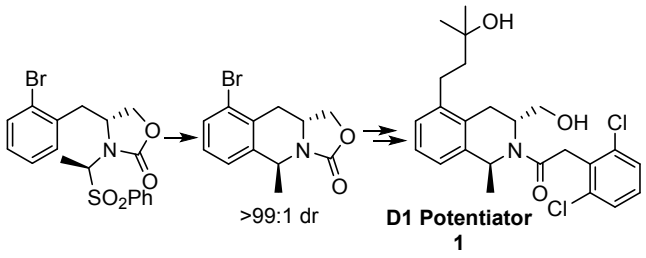
Supporting Information Placeholder



ABSTRACT: A practical synthesis of a D1 potentiator chiral tetrahydroisoquinoline has been accomplished employing diastereoselective Pictet-Spengler methodology to access the required trans-stereochemistry. A dynamic kinetic resolution by crystallization gives high yields of a *N*-(phenylsulfonyl)alkyloxazolidinone that is converted to an acyl iminium ion when exposed to a variety of Lewis acids resulting in a highly diastereoselective Pictet-Spengler cyclization. An eight-step linear synthesis that starts with commercially available *R*-2-bromophenylalanine affords the chiral tetrahydroisoquinoline **1** in 54% overall yield.

The D1 and D2 dopamine receptors are involved with reward and motor activity.[1a, 1b] However, the D1 receptor plays a specific role in the maintenance of higher cognitive functions such as attention, executive function, and working memory.[1a, 1b] The chiral tetrahydroisoquinoline (THIQ) **1**, illustrated in Figure 1, is currently in Phase 2 clinical trials for the treatment of Lewy Body Dementia with a possible unique mechanism of action as a D1 positive allosteric modulator.[2a, 2b, 2c]

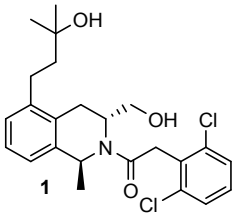
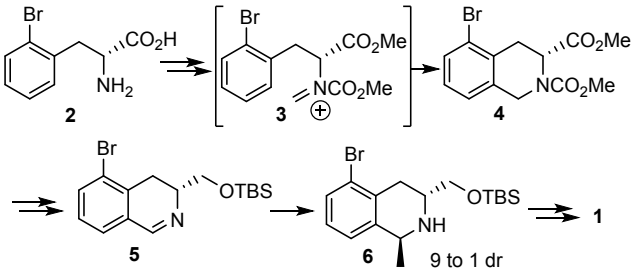


Figure 1. Tetrahydroisoquinoline D1 Potentiator **1**.

The published syntheses of THIQ **1** start with (*R*)-2-bromo-phenylalanine **2** and require 14 reactions with about 17% overall yield.[2a, 2b, 2c] The syntheses begin with conversion of amino-acid **2** to an ester-carbamate, formaldehyde derived, acyl iminium ion **3** to promote a Pictet-Spengler cyclization under classical Bronsted-Lowry acidic conditions to give the THIQ **4**, Scheme 1. Attempts to promote a similar Pictet-Spengler cyclization with acetaldehyde to directly install the required methyl group and stereocenter gave poor yields and no diastereoselectivity. Therefore, THIQ **4** was taken through several functional group manipulations to arrive at the dihydroisoquinoline **5**, which can be reacted with either methyl magnesium chloride or methyl lithium to effect a diastereoselective 1, 2-addition favoring the required trans-diastereomer of the THIQ **6**, which was progressed to THIQ **1** through standard chemical transformations. The continued development and clinical evaluations of THIQ **1** led to the need to develop a shorter and more efficient synthesis.

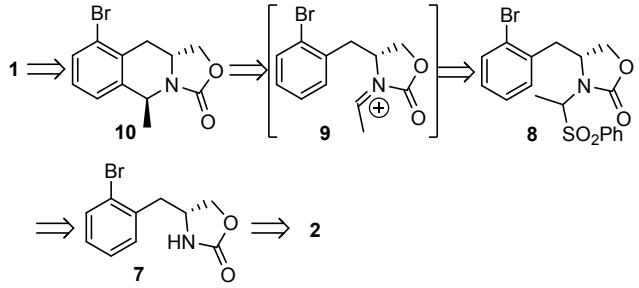
Scheme 1. Intermediates for Diastereoselective 1,2-Addition Based Synthesis of Tetrahydroisoquinoline **1**.



The Pictet-Spengler methodology developed by Petrini[3a, 3b, 3c] and others,[3d, 3e] and adopted by Laschat,[4] for preparing chiral THIQs with high trans-diastereoselectivity appeared to be an

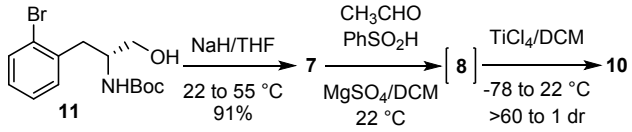
attractive approach for the synthesis of THIQ **1**. This approach is illustrated in the Scheme 2 retrosynthetic plan where the oxazolidinone **7** derived from (*R*)-2-bromo-phenylalanine **2** would be reacted with acetaldehyde and phenylsulfinic acid to give *N*-(phenylsulfonyl)alkyloxazolidinone **8**. Following the Petrini method, *N*-(Phenylsulfonyl)alkyloxazolidinone **8** would be reacted with $TiCl_4$ under cryogenic conditions to form the acyl iminium ion **9** to promote a trans-selective Pictet-Spengler cyclization giving THIQ **10** which would serve as a suitable synthetic precursor to THIQ **1**.

Scheme 2. Retrosynthetic Plan for Tetrahydroisoquinoline **1**.



When the known *tert*-butyl carbamate amino-alcohol **11**[5] was reacted with NaH the oxazolidinone **7** was produced in 91% yield, Scheme 3. Following conditions described by Petrini,[3] oxazolidinone **7** was reacted with acetaldehyde and phenylsulfinic acid in the presence of $MgSO_4$ in DCM for about 3.5 days to produce the *N*-(phenylsulfonyl)alkyloxazolidinone **8** as a mixture of diastereomers. The hydrated $MgSO_4$ was removed by filtration and the resulting mixture cooled to -78 °C and treated with the prescribed 3.5 equivalents of $TiCl_4$.[3] No Pictet-Spengler cyclization was observed under cryogenic conditions, so the reaction was warmed to 22 °C which produced primarily THIQ **10** with greater than 60 to 1 dr (The absolute stereochemistry of the major isomer was confirmed by single crystal X-ray crystallography. CCDC: 1965369). With this method of inducing a diastereoselective Pictet-Spengler cyclization being viable, more practical methods for synthesizing the oxazolidinone **7** and *N*-(phenylsulfonyl)alkyloxazolidinone **8** were desirable.

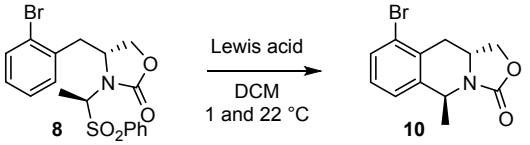
Scheme 3. Diastereoselective Pictet-Spengler Cyclization.



Direct reduction of (*R*)-2-bromo-phenylalanine **2** with borane[6] gave the corresponding known amino-alcohol **12**,[7] Scheme 4. After the reaction was worked-up, diethyl carbonate and K_2CO_3 were added to the crude product solution followed by heating to drive-off EtOH generating the oxazolidinone **7** which was isolated in 84% overall yield. The oxazolidinone **7** was combined with acetaldehyde, sodium benzenesulfinate, water, and formic acid in a sealed reactor which was heated at 60 °C for 24 h causing a single diastereomer of *N*-(phenylsulfonyl)alkyloxazolidinone **8** to crystallize in 95% yield via dynamic kinetic resolution (DKR) (The absolute stereochemistry was confirmed by single crystal X-ray crystallography. CCDC: 1965368).[8] Obtaining a single diastereomer of **8** via a crystallization driven DKR is not imperative for a diastereoselective Pictet-Spengler cyclization since the phenylsulfonyl bearing stereocenter is destroyed during the acyl iminium ion formation. However, the DKR produces a single crystalline diastereomer affording high isolated yields of **8** which cannot be achieved from a diastereomeric mixture.

Highly pure crystalline *N*-(phenylsulfonyl)alkyloxazolidinone **8** was produced using the chemistry detailed in Scheme 4 which gave the opportunity to screen Lewis acids, solvents, and temperature effects for the diastereoselective Pictet-Spengler cyclization to produce THIQ **10**, Table 1. A brief survey of alternative solvents for the Pictet-Spengler cyclization revealed that solvents containing heteroatoms (examples: THF, ether, acetonitrile) shutdown the Lewis acid catalysis and aromatic solvents like toluene competitively attacked the intermediate acyl-iminium ion, so DCM was maintained as the solvent of choice. The crystalline single diastereomer of **8** had poor solubility in DCM under cryogenic conditions causing the Pictet-Spengler cyclization to be severely retarded, so 1 °C and 22 °C reaction temperatures were evaluated for comparative purposes. Under standardized screening conditions, 2.5 equivalents of $TiCl_4$ were required to complete the conversion of **8** to **10** with >90:1 dr at 1 °C with a sharp decrease in dr to >25:1 at 22 °C. $ZrCl_4$ and $HfCl_4$ consistently gave high dr at 1 °C and 22 °C and had a slightly cleaner reaction profile and didn't impart any color to the reaction and product **10** relative to $TiCl_4$. In addition, the equivalents of $ZrCl_4$ could be reduced to 1.95 while still giving complete and clean conversion of **8** to **10**. Zirconium(IV) chloride is a dense free flowing white powder that is easy to handle with cheaper technical grades containing $HfCl_4$ that gave similar results to high purity $ZrCl_4$ for conversion of **8** to **10**.

Table 1. Lewis Acid Screen for Diastereoselective Conversion of Single Diastereomer of **8** to **10**.[1, 2]

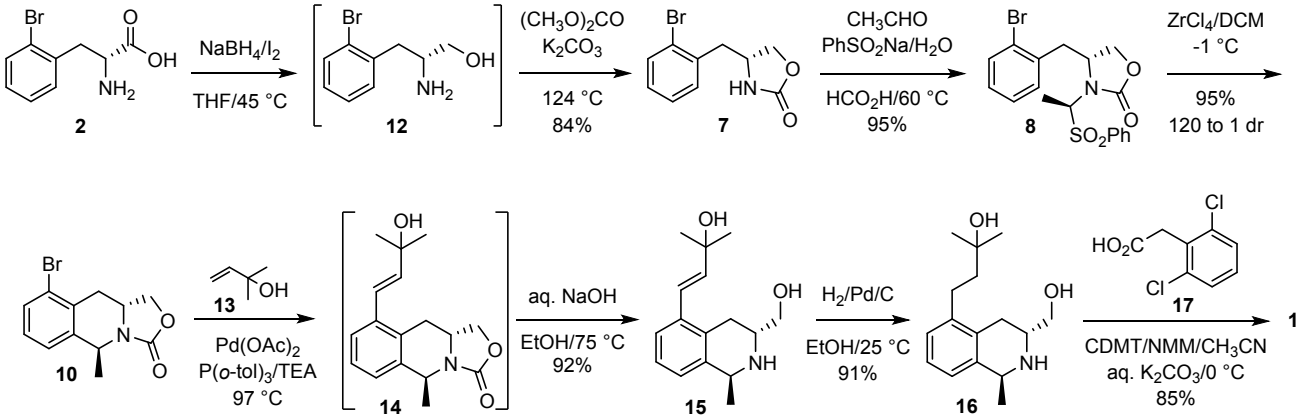


Lewis acid	dr[2] at 1 °C	dr at 22 °C
$TiCl_4$	>90:1	>25:1
$ZrCl_4$	>70:1	>45:1
$HfCl_4$	>50:1	>50:1
BCl_3	no conversion to **10**	no conversion to **10**
$AlCl_3$	>10:1	>8:1
$GaCl_3$	>25:1	>15:1
$InCl_3$	no conversion to **10**	no conversion to **10**

1) Standard conditions: 200 mg of **8** in DCM at 0.12 molar concentration, 2.5 equivalents of Lewis acid added at the stated temperature.
2) 2 h after Lewis acid addition, reaction sample quenched into DMSO-D_6 to assess conversion to **10** and dr by ^1H NMR. Note: where dr is stated the conversion of **8** was >99.5%.

In Scheme 4, the *N*-(phenylsulfonyl)alkyloxazolidinone **8** was dissolved in DCM at a concentration of 0.08 M providing more solvent volume to adsorb the mild exotherm of the Lewis acid addition which resulted in a higher dr than what was observed in the screening reactions that were run at higher concentration (Table 1). The resulting mixture was cooled to -1 °C and 1.95 equivalents of $ZrCl_4$ was added to afford THIQ **10** in 95% yield with 120 to 1 dr.

Scheme 4. Diastereoseletive Pictet-Spengler Cyclization Based Synthesis of D1 Potentiator Tetrahydroisoquinoline **1**.



The subsequent Heck coupling, run in neat 2-methyl-3-buten-2-ol **13**, converted THIQ **10** into the allylic alcohol intermediate **14** which was contaminated with tris-(*o*-tolyl)phosphine and tris-(*o*-tolyl)phosphine oxide.[9a, 9b] The phosphines were poisonous towards palladium catalysis which was required to hydrogenate the newly installed carbon-carbon double bond. Therefore, the oxazolidinone of intermediate **14** was hydrolyzed in situ to reveal the secondary amine of **15** enabling selective extractions to remove phosphines and give a 92% yield across 2 steps. Hydrogenation of allylic alcohol **15** gave the saturated tertiary alcohol **16** in 91% yield. Due to the amine of **16** being sterically encumbered, the final amide-coupling had issues with N vs. O-selectivity with the primary alcohol getting acylated to produce the corresponding ester. In addition, THIQ **1** has restricted rotation about the amide bond (rotamers) due to the flanking chiral centers, which can cause intramolecular rearrangement of the amide to the ester of the primary alcohol to relieve steric compression. High or low pH and/or elevated temperature can cause the rearrangement. We found that a selective amide coupling could be achieved when 2,6-dichlorophenylacetic acid **17** was reacted with 2-chloro-4,6-dimethoxy-1,3,5-trazine (CDMT) that was pre-activated with *N*-methylmorpholine (NMM), followed by addition of amine **16** and aqueous K_2CO_3 to produce the D1 potentiator THIQ **1** in 85% yield.[10]

In conclusion, a practical synthesis of the D1 potentiator chiral tetrahydroisoquinoline **1** has been accomplished employing diastereoselective Pictet-Spengler methodology to access the required trans-stereochemistry. A dynamic kinetic resolution by crystallization affords high yields of *N*-(phenylsulfonyl)alkyloxazolidinone **8** that is converted to an acyl iminium ion when exposed to a variety of Lewis acids resulting in an exquisitely diastereoselective Pictet-Spengler cyclization to give the chiral tetrahydroisoquinoline **10**. The scope of Lewis acids that are useful for this type of diastereoselective Pictet-Spengler cyclization have been expanded during this research. Lastly, the eight-step linear diastereoselective synthesis described in Scheme 4, that starts with commercially available *R*-2-bromophenylalanine, produces the D1 potentiator tetrahydroisoquinoline **1** in 54% overall yield which greatly improves access to this molecule for further development and evaluation in the clinic.

EXPERIMENTAL SECTION

General: ^{1}H and ^{13}C NMR spectra for compound characterization were obtained on a Varian 600MHz DD2 console. ^{1}H NMR spectra to assess reaction conversion and diastereomer ratio for the Table 1 reactions was obtained on a Bruker 500MHz Avance III. Proton fine splitting reported as follows: (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, dd = doublet of doublets, dt = doublet of triplets). Chemical shifts were referenced on residual solvent peaks: DMSO $(CD_3)_2SO$ (δ = 3.33 ppm for ^{1}H NMR and 39.51 ppm for ^{13}C NMR). High resolution mass spectra were measured on a Thermo Scientific LTQ-Orbitrap Discovery using electrospray ionization mode (ESI+) with a mass accuracy greater than 2 ppm, and an applied mass range from 75 to 1500 Da. IR spectra (4000–400 cm^{-1}) were collected and performed by ATR-FTIR (Attenuated Total Reflectance) on a Nicolet 6700 FT-IR with a Smart OMNI sampler on neat solid samples. DSC was performed on a TA SA+ Discovery series instrument running TRIOS Explorer software (10 °C/min). HPLC conditions for monitoring the following reactions: Column: X-Bridge C18, 2.5 µm, 3 mm x 75 mm; mobile phases: 5 mM ammonium formate, adjusted to pH 9 with ammonium hydroxide (A), Acetonitrile (B); gradient program: 0 min (95/5) – 11.25 min (5/95) – 13.50 min (5/95) – 13.61 min (95/5) – 15.75 min (95/5); injection volume 2 uL; column temperature 40 °C; wavelength 220 nm; flow rate 0.8 mL/min. All reactions were run under a nitrogen atmosphere unless otherwise stated.

(R)-4-(2-bromobenzyl)oxazolidin-2-one (7). A 60% dispersion of NaH in mineral oil (63 mg, 1.6 mmol) was added to *tert*-butyl (R)-(1-(2-bromophenyl)-3-hydroxypropan-2-yl) carbamate **11** (0.5 g, 1.5 mmol) in THF (7.5 mL) and the mixture was stirred at 22 °C for 16.5 h. The reaction mixture was warmed with a heating mantle to 55 °C for 45 min and cooled back to 22 °C. The resulting solids were filtered and washed with heptane, followed by dissolving the solids in a mixture of DCM and aqueous NH_4Cl. The layers were separated, the organic phase was collected, and the aqueous phase extracted with DCM. The organic phases were combined, dried over Na_2SO_4, and concentrated under reduced pressure to give **7** (356 mg; 91%) as a white solid.

Alternative procedure for preparing **(R)-4-(2-bromobenzyl)oxazolidin-2-one (7)** based on the safer generation of borane in situ as described in this communication: Lanchi, V.; Ciula, J.; Gooding, O. W. *Org. Process Res. Dev*. **2003**, *7*, 514 (Note: borane is a hazardous chemical).

(R)-4-(2-bromobenzyl)oxazolidin-2-one (7). (R)-2-Bromophenylalanine (170.1 g, 696.9 mmol) and THF (1.7 L) were combined, cooled to 5 °C, and $NaBH_4$ (63.3 g, 1.7 mol) was added in portions to maintain the temperature at less than or equal to 5 °C. A solution of I_2 (176.9 g, 696.9 mmol) in THF (510 mL) was added to the mixture slowly, maintaining the internal reaction temperature at less than 10 °C. The reaction mixture was warmed to RT and then heated with a mantle to 45 °C with stirring for 30 min. MeOH (134.0 g, 4.2 mol) was added dropwise to the reaction mixture. The resulting mixture was concentrated via distillation until the internal temperature reached 68 °C at 700 Torr. To the reaction mixture was added THF (240 mL), aqueous KOH (85% KOH: 46.0 g, 696.9 mmol and water: 150 mL) and toluene (1.7 L). The biphasic mixture was heated until the lower phase reached 83 °C and the mixture was held for 4 h. After cooling to RT, the resulting mixture was washed with 20% aqueous NaCl (3 x 400 mL). The organic phase was concentrated until 90 °C under 200 Torr was reached.

To the resulting concentrated mixture, diethyl carbonate (330.8 g, 2.8 mol) and K_2CO_3 (9.7 g, 69.7 mmol) were added. The resulting mixture was stirred and EtOH was distilled at reflux temperature (bath temperature 145 °C, inner temperature 124 °C) under atmospheric pressure for 3.5 h. The mixture was diluted with isopropyl acetate (850 mL), washed with water (3 x 350 mL), and concentrated to give a slurry of white solids. To the slurry was added isopropyl acetate (340 mL) at 70 °C giving a homogeneous mixture, and heptane (510 mL) was added slowly to the clear solution to crystallize the product. The resulting slurry was cooled to -10 °C, stirred for 1 h, and the solids collected by filtration. The solids were dried at 50 °C under 20 Torr to afford the title compound (151.8 g, 84% yield) with >99% ee by chiral HPLC. $[\alpha]^{20}_D$ 18.8 (MeOH, *c* = 0.2). mp (DSC) (10 °C/min) onset 109.49 °C, maximum 110.00 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.83 (s, 1H), 7.59 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.37 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.32 (td, *J* = 7.4, 1.3 Hz, 1H), 7.18 (td, *J* = 7.6, 1.8 Hz, 1H), 4.27 (t, *J* = 8.2 Hz, 1H), 4.12 – 4.04 (m, 1H), 4.02 (dd, *J* = 8.4, 5.2 Hz, 1H), 2.98 (dd, *J* = 13.7, 5.8 Hz, 1H), 2.86 (dd, *J* = 13.7, 7.5 Hz, 1H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 158.9, 136.4, 133.1, 132.2, 129.3, 128.3, 124.6, 68.4, 51.7, 40.8. IR (ATR) 3246, 3140, 2923, 1757, 1472, 1444, 1408, 1247 cm^{-1}. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{10}H_{11}BrNO_2$ 255.9968; Found 255.9968.

(4R)-3-[(1S)-1-(benzenesulfonyl)ethyl]-4-[(2-bromophenyl)methyl]oxazolidin-2-one (8). (4R)-4-[(2-bromophenyl)methyl]oxazolidin-2-one **7** (100.0 g, 390.5 mmol), sodium benzenesulfinate (86.0 g, 523.9 mmol), water (500 mL), formic acid (115 mL) and acetaldehyde (95.6 g, 2.2 mol) were charged to a 1 L autoclave. The resulting mixture was heated with a mantle to 60 °C for 24 h to give a slurry that was cooled to 35 °C and filtered. The solids were washed with water (100 mL) and dried at 50 °C under 20 Torr to afford **8** (157.5 g, 95% yield) as a single diastereomer by NMR analysis. Compound **8** was recrystallized from toluene and the absolute stereochemistry of (R)-4-(2-bromobenzyl)-3-((S)-1-(phenylsulfonyl)ethyl)oxazolidin-2-one (**8**) was confirmed by single crystal X-ray analysis (CCDC: 1965368). $[\alpha]^{20}_D$ -109.6 (DMSO, *c* = 0.2). mp (DSC) (10 °C/min) onset 152.26 °C, maximum 153.41 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.90 (d, *J* = 8.5 Hz, 2H), 7.77 (t, *J* = 7.3 Hz, 1H), 7.63 (td, *J* = 8.0, 1.4 Hz, 3H), 7.43 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.36 (td, *J* = 7.5, 1.3 Hz, 1H), 7.22 (td, *J* = 7.7, 1.7 Hz, 1H), 5.24 (q, *J* = 7.2 Hz, 1H), 4.45 (m, 1H), 4.05 (m, 1H), 4.00 (dd, *J* = 8.9, 2.5 Hz, 1H), 3.22 (dd, *J* = 13.5, 3.8 Hz, 1H), 2.81 (dd, *J* = 13.5, 10.7 Hz, 1H), 1.77 (d, *J* = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 156.8, 136.5, 135.6, 135.1, 133.3, 132.9, 130.0, 129.8, 129.3, 128.5, 124.6, 70.3, 66.8, 52.6, 39.7, 12.3. IR (ATR) 3096, 3076, 3055, 2976, 2947, 2929, 1747, 1446, 1402, 1308, 1144 cm^{-1}. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{18}H_{19}BrNO_4S$ 424.0213; Found 424.0211.

(5S,10aR)-9-bromo-5-methyl-1,5,10,10a-tetrahydro-3H-oxazolo[3,4-b]isoquinolin-3-one (10). (4R)-3-[(1S)-1-(benzenesulfonyl)ethyl]-4-[(2-bromophenyl)methyl]oxazolidin-2-one **8** (144.2 g; 339.9 mmol) was combined with DCM (4325 mL) and the resulting mixture cooled to -1 °C. Zirconium(IV) chloride (154.0 g; 660.8 mmol) was added in four portions (38.5 g each) and the resulting mixture was stirred for 2 h. Water (720 mL) and 28% aqueous NH_3 (720 mL) were added slowly to the reaction mixture. The aqueous phase was separated, and the organic phase was washed with water (720 mL). The organic phase was dried over Na_2SO_4 and filtered. The filtrate was concentrated, and the resulting white solid was dried at 50 °C under 20 Torr to afford **10** (91.6 g, 95% yield, 120:1 dr by HPLC). Crystals of **10** were grown via vapor diffusion of heptane into a toluene solution of **10** at RT and the absolute stereochemistry of **10** was confirmed by single crystal X-ray analysis (CCDC: 1965369). $[\alpha]^{20}_D$ 124.9 (MeOH, *c* = 0.2). mp (DSC) (10 °C/min) onset 85.60 °C, maximum 86.25 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.51 (d, *J* = 7.9 Hz, 1H), 7.33 (d, *J* = 7.8 Hz, 1H), 7.17 (t, *J* = 7.8 Hz, 1H), 4.84 (q, *J* = 6.8 Hz, 1H), 4.53 (t, *J* = 8.1 Hz, 1H), 4.19 (dd, *J* = 8.4, 5.3 Hz, 1H), 4.14 (ddt, *J* = 10.4, 8.1, 4.6 Hz, 1H), 3.11 (dd, *J* = 16.6, 4.6 Hz, 1H), 2.57 (dd, *J* = 16.6, 10.4 Hz, 1H),z 1.41 (d, *J* = 6.8 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 156.2, 140.3, 131.8, 131.1, 128.5, 127.1, 125.2, 68.7, 48.2, 47.2, 34.4, 22.1. IR (ATR) 3077, 2979, 2937, 1743, 1562, 1420, 1280 cm^{-1}. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{12}H_{13}BrNO_2$ 282.0124; Found 282.0127.

(E)-4-((1S,3R)-3-(hydroxymethyl)-1-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-2-methylbut-3-en-2-ol (15). Deoxygenated 2-methyl-3-buten-2-ol (109.9 g, 1.3 mol), $Pd(OAc)_2$ (318.3 mg, 1.4 mmol) and tri-*o*-tolylphosphine (2.2 g, 7.2 mmol) were combined and the mixture was stirred at 16 °C for 30 min. To the mixture, (5S,10aR)-9-bromo-5-methyl-1,5,10,10a-tetrahydro-3H-oxazolo[3,4-b]isoquinolin-3-one **10** (80 g, 283.6 mmol) and deoxygenated TEA (43 g, 424.9 mmol) were added, and the resulting mixture was heated with a mantle at 97 °C for 5 h. The reaction mixture was cooled to RT, and EtOH (400 mL) and 50 wt% aqueous NaOH (226.8 g, 2.8 mol) were added to the reaction mixture. The resulting mixture was heated to 75 °C for 3 h, cooled to RT, and filtered. The filtrate was concentrated at 50 °C under 80 Torr. Toluene (400 mL), water (400 mL) and saturated aqueous citric acid (640 mL) were added to the concentrated residue. The organic phase was separated, and the aqueous phase was washed with toluene (400 mL). 50 wt% aqueous NaOH (400 mL) was slowly added to the aqueous phase. The mixture was extracted with isopropyl acetate (2 x 800 mL), and the combined organic phases were dried over Na_2SO_4 and filtered. The filtrate was concentrated at 50 °C under 50 Torr and the residue was dissolved in isopropyl acetate (320 mL) at 60 °C. The resulting mixture was cooled to RT to give a slurry and heptane (1040 mL) was slowly added. The slurry was cooled to -10 °C, stirred for 1 h, and the solids were collected by filtration. The off-white solids were washed with heptane (160 mL) and dried at 50 °C under 20 Torr to afford **15** (68.6 g, 92% yield). $[\alpha]^{20}_D$ -8.9 (MeOH, *c* = 0.2). mp (DSC) (10 °C/min) onset 97.75 °C, maximum 100.58 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.21 (d, *J* = 7.8 Hz, 1H), 7.05 (t, *J* = 7.6 Hz, 1H), 6.95 (d, *J* = 7.6 Hz, 1Hz), 6.66 (d, *J* = 15.8 Hz, 1H), 6.17 (d, *J* = 15.8 Hz, 1H), 4.69 (s, 1H), 4.62 (br, 1H), 4.08 (q, *J* = 6.8 Hz,

1H), 3.46 (dd, *J* = 10.3, 5.1 Hz, 1H), 3.39 (dd, *J* = 10.3, 6.6 Hz, 1H), 3.06 (m, 1H), 2.67 (dd, *J* = 16.4, 4.2 Hz, 1H), 2.24 (dd, *J* = 16.4, 10.1 Hz, 1H), 2.13 (br, 1H), 1.31 (d, *J* = 6.8 Hz, 3H), 1.25 (s, 6H). $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ 141.3, 141.2, 136.5, 131.9, 126.0, 125.5, 123.2, 122.4, 69.9, 65.7, 50.5, 48.9, 30.6, 30.6, 29.5, 24.2. IR (ATR) 3385, 3312, 3284, 3034, 2965, 2919, 2881, 2825, 1582, 1448, 1420, 1376, 1252 cm^{-1}. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{16}H_{24}NO_2$ 262.1802; Found 262.1799.

4-[(1S,3R)-3-(hydroxymethyl)-1-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl]-2-methylbutan-2-ol (16). Under nitrogen, (E)-4-((1S,3R)-3-(hydroxymethyl)-1-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-2-methylbut-3-en-2-ol **15** (50 g, 191.3 mmol), 5% Pd/C (1.09 g (wet wt.), 1.0 wt% (dry wt.)) and EtOH (250 mL) were combined in an autoclave, purged with nitrogen, and the nitrogen was replaced with hydrogen at 145 psig. The resulting mixture was stirred at RT for 4 h under 145 psig of hydrogen. The reaction mixture was filtered over a bed of diatomaceous earth and concentrated at 50 °C under 50 Torr. The resulting solids were collected by filtration and suspended and stirred in isopropyl acetate (200 mL) at RT for 1 h. Heptane (200 mL) was added dropwise, and the resulting slurry was cooled to -10 °C and stirred for 1 h. The resulting solids were collected by filtration, washed with heptane (100 mL), and dried at 50 °C under 20 Torr to afford the title compound (46.2 g, 91% yield, single diastereomer and enantiomer by NMR and HPLC respectively) as a white solid. $[\alpha]^{20}_D$ 19.5 (MeOH, *c* = 0.2). mp (DSC) (10 °C/min) onset 125.85 °C, maximum 127.22 °C. ^1H NMR (600 MHz, DMSO-d_6) δ 7.00 (t, *J* = 7.5 Hz, 1H), 6.91 (d, *J* = 7.4 Hz, 1H), 6.89 (d, *J* = 7.5 Hz, 1H), 4.63 (s, 1H), 4.21 (s, 1H), 4.07 (q, *J* = 6.7 Hz, 1H), 3.46 (dd, *J* = 10.5, 4.9 Hz, 1H), 3.37 (dd, *J* = 10.3, 6.8 Hz, 1H), 3.06 (tt, *J* = 10.4, 4.6 Hz, 1H), 2.64 (dd, *J* = 16.3, 4.1 Hz, 1H), 2.52 (t, *J* = 8.7 Hz, 2H), 2.21 (dd, *J* = 16.3, 10.1 Hz, 1H), 2.08 (s, 1H), 1.57 – 1.45 (m, 2H), 1.31 (d, *J* = 6.8 Hz, 3H), 1.13 (s, 6H). $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ 141.2, 141.2, 132.5, 126.2, 125.4, 124.6, 69.1, 65.7, 50.5, 49.1, 44.7, 29.6, 29.6, 28.8, 27.4, 24.3. IR (ATR) 3376, 3294, 3079, 2973, 2920, 2870, 2826, 2703, 1587, 1479, 1459, 1445, 1378, 1156 cm^{-1}. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{16}H_{26}NO_2$ 264.1958; Found 264.1956.

2-(2,6-dichlorophenyl)-1-[(1S,3R)-3-(hydroxymethyl)-5-(3-hydroxy-3-methyl-butyl)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl]ethenone (1).[2] 2-Chloro-4,6-dimethoxy-1,3,5-triazine (14.7 g, 83.7 mmol) and ACN (400 mL) were combined, and 4-methylmorpholine (17.7 g, 175.0 mmol) was added at 0 °C. The resulting mixture was stirred for 30 min, 2,6-dichlorophenylacetic acid (20.8 g, 101.4 mmol) was added, and the mixture was stirred at 0 °C for 1 h. 4-[(1S,3R)-3-(hydroxymethyl)-1-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl]-2-methylbutan-2-ol **16** (20 g, 75.9 mmol) and a mixture of K_2CO_3 (11.5 g, 83.7 mmol) in water (100 mL) were added to the mixture and stirred for 4 h at 0 °C. The resulting layers were separated, and the organic phase was diluted with isopropyl acetate (100 mL) and saturated aqueous NH_4Cl (100 mL). The resulting layers were separated, and the organic phase was washed with water (100 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated at 50 °C under 80 Torr and the resulting mixture was dissolved in isopropyl acetate (80 mL). The resulting mixture was cooled to RT, heptane (80 mL) was added dropwise, and the resulting slurry was cooled to -10 °C with stirring for 1 h. The resulting solids were collected by filtration, washed with heptane (40 mL), and dried at 50 °C under 20 Torr to obtain the title compound (29.2 g, 85% yield).

SUPPORTING INFORMATION

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