Note

An Expedient Synthesis of Furo[2,3-d][1,3]thiazinamines and Pyrano[2,3-d][1,3]thiazinamines from Enones and Thiourea

Yong-Jin Wu, Jason Guernon, Hyunsoo Park, and Lorin A. Thompson

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An Expedient Synthesis of Furo[2,3-*d*][1,3]thiazinamines and Pyrano[2,3-*d*][1,3]thiazinamines from Enones and Thiourea

Yong-Jin Wu,* Jason Guernon, Hyunsoo Park, Lorin A. Thompson

Research and Development, Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, CT 06492, USA

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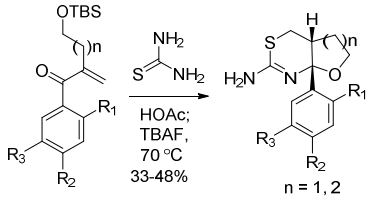


ABSTRACT: Michael addition of thiourea to enones with subsequent intramolecular aminal ether formation provided easy access to furo[2,3-*d*]thiazinamines and pyrano[2,3-*d*][1,3]thiazin-2-amines. These amines served as versatile intermediates to a variety of beta-amyloid cleaving enzyme-1 (BACE1) inhibitors.

There is substantial evidence to suggest that β-amyloid (Aβ) peptide, particularly the longer 42 amino acid form, Aβ42, plays a critical role in the progression of Alzheimer's disease (AD).[1-4] Aβ is derived from the β-amyloid precursor protein (APP) by proteolysis. Cleavage of APP by β-site APP cleaving enzyme-1 (BACE1) results in shedding of the APP ectodomain, and the remaining membrane bound C-terminal fragment, C99, is further processed by γ-secretase to produce Aβ. Thus, inhibition of BACE1 to reduce Aβ production is a promising approach to test the amyloid hypothesis.[5-7] Recently, scientists from Eli Lilly reported the discovery of tetrahydro-4H-furo[3,4-*d*][1,3]thiazin-2-amine **1** (LY2886721, Figure 1), a potent BACE1 inhibitor that reached phase II clinical trials in mild congitive impairmente.[8] The fused bicyclic ring system was constructed through a stepswise process: intramolecular nitrile oxide-olefin cycloaddition to form the furan ring and intramolecular Mitsunobu reaction of the *N*-benzoylthiourea intermediate **5** to form the 6-membered thiazinamine ring (Scheme 1).[9] As part of our continuous efforts in the discovery of BACE1 inhibitors, we sought to design close analogs of **1** where the fused bicyclic ring system can be assembled more efficiently in one single operation. An X-ray co-crystal structure of **1** bound in the BACE1 active site indicates no particular interaction with the furan oxygen,[8] and therefore relocation of the furan oxygen to the adjacient position as shown in **2** (Figure 1)

would be expected to have marginal impact on activity. Retrosynthetically, the furo[2,3-*d*]thiazinamine intermediates **7a/b** could be assembled from 4-hydroxybutyl carbamimidothioate ketones **8a/b** via an intramolecular aminal ether formation. Compounds **8a/b** can be visualized from the Michael addition of enones **9a/b** with thiourea (Scheme 2). This report describes our endeavors in this area.

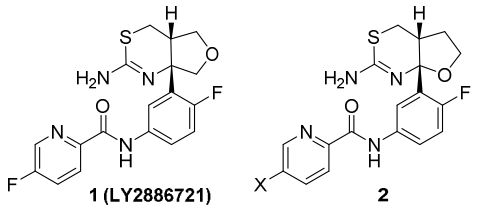
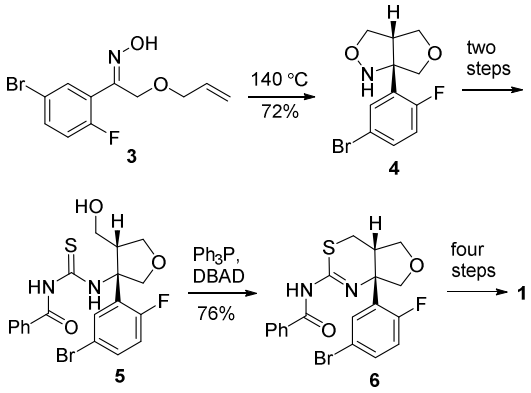
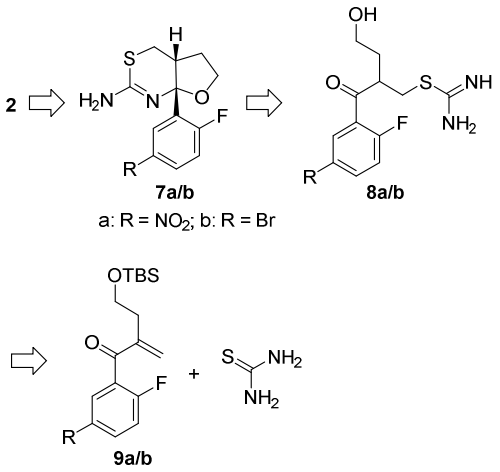


Figure 1. Structures of BACE-1 inhibitors

Scheme 1. Synthesis of furo[3,4-*d*][1,3]thiazin-2-amine **1**



Scheme 2. Retroynthesis of furo[2,3-*d*][1,3]thiazinamine **2**



Our synthesis started with vinyl bromide **10**[10] which was readily prepared from commercially availble 3-bromobut-3-en-1-ol under standard silylation conditions (Scheme 3). Lithium-halogen exchange of **10** with *tert*-butyllithium provided the vinyl lithium reagent which was added to 2-fluoro-5-nitrobenzaldehyde to furnish allylic alcohol **11** in 31% yield. This alcohol was converted to enone **9a** by Swern oxidation or upon treatment with manganese dioxide. This enone was treated with thiourea in acetic acid at room temperature. LCMS analysis of the crude product using TFA as a solvent modifier showed clean conversion, while a similar analysis using a mildly basic ammonium acetate modifier showed evidence of instability through retro-Michael addition. Efforts to purify the Michael adduct **12** by either silica gel chromatograhy or recrystallization failed again due to *retro*-Michael addition. For this reason, the crude reaction mixture in acetic acid was treated with tetrabutylammonium fluoride (TBAF). As the deprotection was somewhat sluggish at room temperature, the reaction mixture was then warmed to 70 ºC, and the *tert*-butylsilyl ether was cleaved within 10 min. Heating this crude reaction mixture at 70 ºC for 10 h resulted in smooth ring closure to **7a** as shown by LC/MS analysis. For our medicinal chemistry program, we desired to have enantiomerically pure intermediates. Thus, we attempted preparative chiral HPLC separation of racemic **7a** without success. Therefore, the crude **7a** was subjected to Boc protection to give (±)-**13**. Chiral supercritical fluid chromatography (SFC) on (±)-1**3** gave (*R*,*R*)-**13** and (*S*,*S*)-**13** in 14% and 19% yield, respectively from **9a** on a 11 g scale. Assuming an 85% yield for the Boc protection reaction, the three-step, one-pot process proceeds in 40% yield. This throughput was more than sufficient for analoging. The absolute configurations of both enantiomers were confirmed by single-crystal X-ray diffraction analysis (Figure **2**).[11]

Scheme 3. Synthesis of furo[2,3-*d*][1,3]thiazinamine **7a**

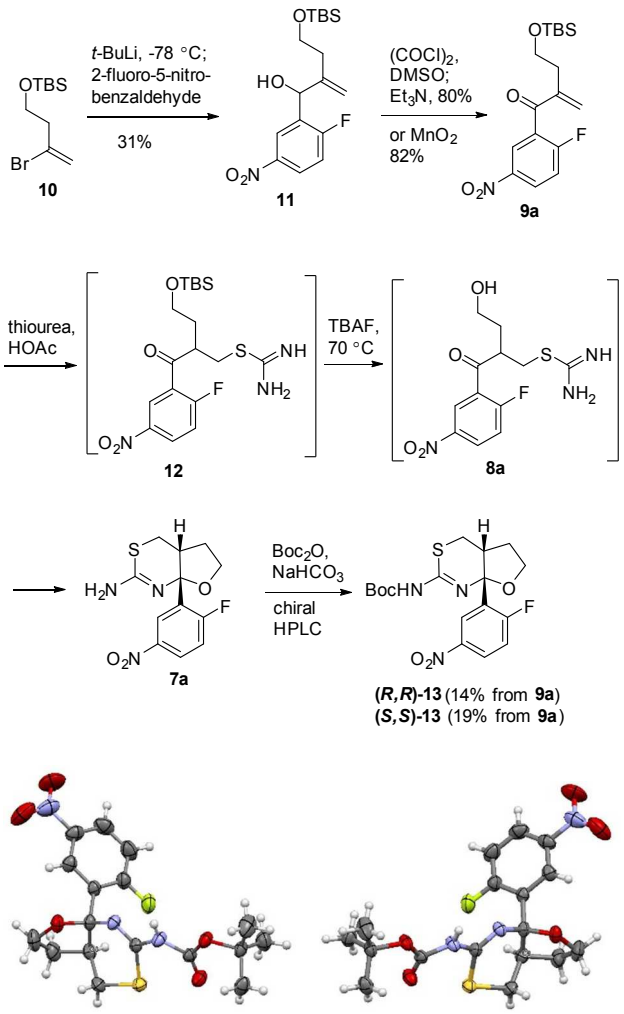
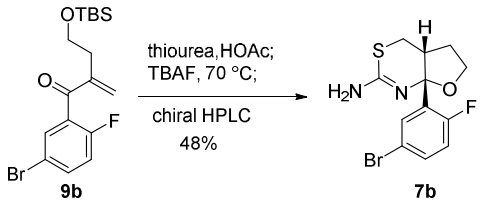


Figure 2. Thermal ellipsoid plots (50% ellipsoids) of (*S*,*S*)-**13** (left) and (*R*,*R*)-**13** (right).

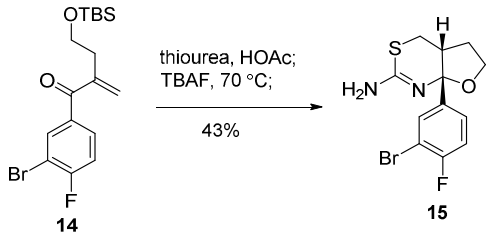
Enone **9b** was converted to the bicyclic compound **7b** in the same fashion as **9a** was converted to **7a** (Scheme 4). In this case, we were able to carry out preparative chiral HPLC separation of (±)-**7b**, and the two enantiomers of **7b** were obtained independently in a combined yield of 48%.

Scheme 4. Synthesis of furo[2,3-*d*][1,3]thiazinamine **7b**



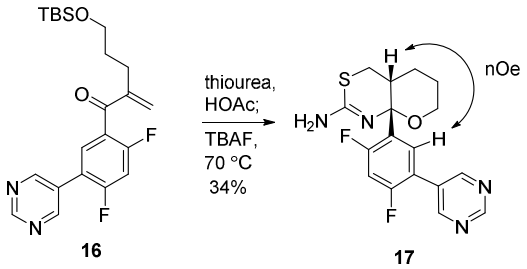
In order to probe the impact of the fluorine substitution on both BACE1 inhibitory activity and pharmaceutical properties, we also prepared furo[2,3-*d*]thiazinamines with fluorine substitution of the phenyl ring at the para position (**15**) from enone **14** (Scheme 5). This reaction was run only once, and the yield shown was not optimized.

Scheme 5. Synthesis of furo[2,3-*d*][1,3]thiazinamines **15**



This methodology was extended to the synthesis of pyrano[2,3-*d*][1,3]thiazin-2-amines. For example, treatment of enone **16** with thiourea followed by TBAF and heating under typical conditiones provided a single fused bicyclic compound **17** in 33% yield. The *cis*-fused stereochemistry was assigned based on the nOe effect observed between the angular hydrogen and the hydrogen attached to the difluorophenyl ring (Scheme 6). More studies are required to understand the high stereoselectivity observed in the intramolecular aminal ether formation.

Scheme 6. Synthesis of pyrano[2,3-*d*][1,3]thiazinamine **17**



In summary, we have developed an operationally simple three-step, one pot procedure for the synthesis of furo[2,3-*d*][1,3]thiazinamines and pyrano[2,3-*d*][1,3]thiazinamines. These amines were incorporated into a variety of BACE1 inhibitors, and the biological data for these compounds will be reported in due course.

EXPERIMENTAL SECTION

General. All non-aqueous reactions were carried out under an argon or nitrogen atmosphere at room temperature, unless otherwise noted. All commercial reagents and anhydrous solvents were purchased from commercial sources and were used without further purification or distillation, unless otherwise stated. Analytical thin layer chromatography (tlc) was performed on silica gel 60 F254 (0.25 mm). Compounds were visualized by UV light and/or stained with either p-anisaldehyde, potassium permanganate, or cerium molybdate solutions followed by heating. Flash column chromatography was performed using SiO_2 columns of the appropriate sizes, with gradients of solvents as indicated. Analytical high pressure liquid chromatography (HPLC) and LC-MS analyses were conducted using a single piston pump and a UV-vis detector set at 220 nm or 254 nm with MS detection performed with a LC spectrometer. Chiral LC/Analytical SFC conditions: Column: Lux-Cellulose-2 (0.46 x 25cm), Mobile phase: 10% methanol in CO_2, Flow rate: 3 mL/min, wavelength: 220 nm; Temp.: 35 °C. Preparative SFC chromatography: Lux-Cellulose-2 (3 x 25cm), 8% methanol in CO_2, 140 mL/min at 220 nm and 35°C; Sample in methanol, conc. = 70 mg/mL, Stack injection: 0.5 mL/9.2min. Fractions containing product were concentrated, and dried overnight under vacuum to provide desired compounds. High resolution mass spectrometry (HRMS) analyses were performed on a Fourier Transform Orbitrap mass spectrometer in positive or negative electrospray ionization mode (ESI) operating at 100,000 resolution (full width at half height maximum, FWHM). The instrument was daily calibrated according to manufacturer's specifications resulting in mass accuracy of or better than 5 ppm. NMR (^{1}H and ^{13}C) spectra were recorded on 500 MHz or 400 MHz spectrometers and calibrated using an internal reference.

(3-Bromobut-3-enyloxy)(*tert*-butyl)dimethylsilane (10).[10] To a solution of 3-bromobut-3-en-1-ol (5.2 g, 34.4 mmol) in dichloromethane (69 mL) at rt was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (10 g. 37.9 mmol) and Hunig's base

(7.22 mL, 41.3 mmol), and the mixture was stirred at rt for 30 min. Water was added, the aqueous layer was extracted with dichloromethane (x3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and then filtered. The filtrate was evaporated in vacuo, and the resulting crude product was purified by silica gel chromatography eluting with 5-30% ethyl acetate/hexanes to give **10** as a colorless liquid (8.72 g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.66 (1H, s), 5.48 (1H, s), 3.81 (2H, t, J = 6.0 Hz), 2.64 (2H, t, J = 6.0 Hz), 0.91 (9H, s), and 0.09 (6H, s).

4-(*tert*-Butyldimethylsilyloxy)-1-(2-fluoro-5-nitrophenyl)-2-methylenebutan-1-ol (11). To a solution of **10** (3.14 g, 11.83 mmol) in THF (10 mL) at -78 °C was added *tert*-butyllithium (14.8 mL, 23.7 mmol, 1.7 M solution in hexanes) dropwise over a period of 5 min, and the reaction mixture was stirred at -78 °C for 10 min. The resulting lithium reagent was added dropwise to a solution of 2-fluoro-5-nitrobenzaldehyde (2 g, 11.8 mmol) in THF (10 mL) at -78 °C, and the reaction mixture was stirred at -78 °C for 30 min. Water was added, the aqueous layer was extracted with ethyl acetate (x3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and then filtered. The filtrate was evaporated in vacuo, and the resulting crude product was purified by silica gel chromatography eluting with 0-25% ethyl acetate//hexanes to give **11** as a colorless oil (1.3 g, 31% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.57 (1H, m), 8.18 (1H, m), 7.15 (1H, m), 5.52 (1H, br. s), 5.16 (1H, s), 5.09 (1H, s), 4.96 (1H, m), 3.7-3.9 (2H, m), 2.20-2.35 (2H, m), 0.97 (9H, s), 0.17 (3H) and 0.15 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ (attached protons) -5.5 (2C, 3), 18.4 (0), 25.9 (3C, 3), 34.6 (2), 64.7 (2), 70.5 (1), 116.1 (1) (d, J = 25.1 Hz). 116.2 (2), 124.3 (1) (d, J = 7.5 Hz), 124.5 (1) (d, J = 10.1 Hz), 132.7 (0) (d, J = 14.7 Hz), 144.4 (0), 147.2 (0), and 163.3 (0) (d, J = 258.3 Hz). LCMS m/z: 338.2 $(M + H)^+$. HRMS m/z (ESI) calcd for $C_{17}H_{25}O_3NFSi$ $(M + H - H_2O)^+$ 338.1587, found 338.1582.

4-(*tert*-Butyldimethylsilyloxy)-1-(2-fluoro-5-nitrophenyl)-2-methylenebutan-1-one (9a). Method 1: To a solution of oxalyl chloride (1.1 mL, 12.7 mmol) in DCM (30 mL) at -78°C was added DMSO (0.9 mL, 12.7 mmol), and the reaction mixture was stirred at -78°C for 20 min. A solution of **11** (3 g, 8.4 mmol) in DCM (30 mL) was added, and the reaction mixture was stirred at -78°C for 20 min. Triethylamine (5.9 mL, 42.2 mmol) was added, and the reaction mixture was warmed up to RT and stirred at RT for 30 min. Water was added and the aqueous layer was extracted with ethyl acetate (x3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated in vacuo to give the crude product. The crude product was purified by silica gel chromatography eluting with 0-10% ethyl acetate/hexanes to give **9a** (2.4 g, 80%). Method 2: To a solution of **11** (0.94 g, 2.64 mmol) in chloroform (88 mL) was added manganese dioxide (3.45 g, 39.7 mmol), and the reaction mixture was heated under reflux for 24 h. The reaction mixture was filtered through a pad of Celite, and the filtrate was evaporated in vacuo. The residue was purified by silica gel chromatography eluting with 5-10% ethyl acetate/hexanes to give **9a** as a colorless oil (0.77 g, 82% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.35 (1H, m), 7.35 (1H, m), 6.18 (1H, s), 5.76 (1H, s), 3.83 (2H, t, J = 6.0 Hz), 2.72 (2H, t, J = 6.0 Hz), 0.90 (9H, s), and 0.08 (6H, s). ^{13}C NMR (125 MHz,

$CDCl_3$): δ (attached protons) -5.4 (2C, 3), 18.3 (0), 25.9 (3C, 3), 34.2 (2), 61.4 (2), 117.4 (1) (d, J = 24.4 Hz), 126.2 (1) (d, *J* = 5.3 Hz), 127.7 (1) (d, *J* = 10.3 Hz), 128.3 (0) (d, *J* = 18.0 Hz), 131.7 (2), 143.9 (0), 145.8 (0), 162.5 (0) (d, *J* = 262.6 Hz), 192.1 (0). HRMS m/z (ESI) calcd for $C_{17}H_{25}O_4NFSi$ $(M + H)^+$ 354.1537, found 354.1531.

(4a*RS*,7a*RS*)-7a-(2-Fluoro-5-nitrophenyl)-4a,5,6,7a-tetrahydro-4H-furo[2,3-d][1,3]thiazin-2-amine ((±)-7a). To a solution of **9a** (11 g, 31.1 mmol) in acetic acid (110 mL) was added thiourea (9.5 g, 124 mmol) at rt, and the reaction mixture was stirred at rt for 5 h. TBAF (1 M in THF) (46.7 mL, 46.7 mmol) was added, and the reaction mixture was heated at 70 °C for 12 h. Acetic acid was removed under reduced pressure, saturated sodium bicarbonate was added, and the aqueous layer was extracted with ethyl acetate (x3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and then filtered. The filtrate was evaporated to give 11 g of the crude product, which was used directly for the Boc protection reaction. A small fraction of the crude product was purified by preparatibe TLC eluting with 90% DCM/9% MeOH/1% $NH_3 \bullet H_2O$ to give (±)-**7a** as colorless oil for analytical data. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.56 (dd, *J* = 6.8, 3.0 Hz, 1H), 8.26 - 8.14 (m, 1H), 7.19 (dd, *J* = 10.2, 8.9 Hz, 1H), 4.11 (t, *J* = 7.2 Hz, 2H), 3.16 - 3.08 (m, 1H), 3.05 - 2.93 (m, 1H), 2.78 - 2.67 (m, 1H), 2.30 - 2.13 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) (attached protons) δ 163.1 (0) (d, *J* = 258 Hz), 153.0 (0), 143.7 (0) (d, *J* = 2.0 Hz), 133.5 (0) (d, *J* = 12 Hz), 125.0 (1) (d, *J* = 9.0 Hz), 124.2 (1) (d, *J* = 5.0 Hz), 117.1 (1) (d, *J* = 26 Hz), 92.8 (0), 64.5 (2), 36.9 (1), 29.1 (2) and 27.1 (2). HRMS m/z (ESI) calcd for $C_{12}H_{13}O_3N_3FS$ $(M + H)^+$ 298.0655, found 298.0656.

(*R*,*R*)- and (*S*,*S*)-*tert*-Butyl 7a-(2-fluoro-5-nitrophenyl)-4a,5,6,7a-tetrahydro-4H-furo[*2,3-d*][1,3]thiazin-2-ylcarbamate ((*R*,*R*)-13 and (*S*,*S*)-13). The crude (±)-**7a** (11 g) obtained from above was dissolved in dioxane (100 mL), and di-*tert*-butyl dicarbonate (9.4 g, 42.9 mmol), saturated sodium bicarbonate (100 mL) and water (10 mL) were added. The reaction mixture was stirred at rt for 12 h. Water was added, the aqueous layer was extracted with ethyl acetate (x3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and then filtered. The filtrate was evaporated in vacuo, and the resulting crude product was purified by chiral supercritical fluid chromatography (AD column) to give (*S*,*S*)-1**3** (2.2 g, 19% yield) as a white solid and (*R*,*R*)-1**3** (1.6 g, 14% yield) as a white solid. (*S*,*S*)-**13**: retention time: 2.1 min; HRMS m/z (ESI) calcd for $C_{17}H_{21}O_5N_3FS$ $(M + H)^+$ 398.1185, found 398.1180. (*R*,*R*)-**13**: retention time: 3.5 min; (chiral AD-H 250x4.6 mm, CO_2 flow rate: 2.8 mL/min, co-solvent flow rate: 1.2 mL/min, co-solvent: 0.3% Et_2NH in methanol, co-solvent% : 30, total running time: 14 min). ^{1}HNMR (500 MHz, $CDCl_3$): δ 8.51 (1H, m), 8.25 (1H, m), 7.24 (1H, t, *J* = 9.0 Hz), 4.14 (2H, t, *J* = 8.5 Hz), 3.23 (1H, m), 2.90 (2H, m), 2.40 (1H, m), 2.20 (1H, m), and 1.50 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.8, 28.1, 28.9, 65.3, 91.7, 117.8 (d, *J* = 25.4 Hz), , 124.6, 126.1, 144.1, 163.5 (d, *J* = 258.7 Hz). LCMS m/z: 398.1 $(M + H)^+$. HRMS m/z (ESI) calcd for $C_{17}H_{21}O_5N_3FS$ $(M + H)^+$ 398.1185, found 398.1180.

1-(5-Bromo-2-fluorophenyl)-4-((tert-butyldimethylsilyl)oxy)-2-methylenebutan-1-one (9b). Step A: To a solution of **10** (1.57 g, 5.91 mmol) in THF (16 mL) at -78 °C was added *tert*-butyllithium (6.9 mL, 11.8 mmol, 1.7 M solution in hexanes) dropwise over a period of 5 min, and the reaction mixture was stirred at -78 °C for 10 min. The resulting lithium reagent was added dropwise to a solution of 5-bromo-2-fluorobenzaldehyde (1 g, 4.9 mmol) in THF (2 mL) at -78 °C, and the reaction mixture was stirred at -78 °C for 30 min. Water was added, the aqueous layer was extracted with ethyl acetate (x3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and then filtered. The filtrate was evaporated in vacuo, and the resulting crude product was purified by silica gel chromatography eluting with 0-5% ethyl acetate//hexanes to give 1-(5-bromo-2-fluorophenyl)-4-((tert-butyldimethylsilyl)oxy)-2-methylenebutan-1-ol (923 mg, 48% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 - 7.65 (m, 1H), 7.35 (ddd, *J* = 8.7, 4.5, 2.7 Hz, 1H), 6.89 (dd, *J* = 9.8, 8.7 Hz, 1H), 5.45 (br. s., 1H), 5.15 (d, *J* = 0.9 Hz, 1H), 5.04 (s, 1H), 4.48 (d, *J* = 3.5 Hz, 1H), 3.86 - 3.79 (m, 1H), 3.73 (ddd, *J* = 9.6, 8.4, 4.3 Hz, 1H), 2.37 - 2.17 (m, 2H), 1.01 - 0.93 (s, 9H), 0.14 (3H, s) and 0.13 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ (attached protons) -5.5 (2C, 3), 18.4 (0), 25.9 (3C, 3), 34.8 (2), 64.5 (2), 70.5 (1), 115.3 (2), 117.0 (1) (d, *J* = 23.1 Hz), 116.7 (0), 131.0 (1) (d, *J* = 4.5 Hz), 131.4 (1) (d, *J* = 8.2 Hz), 132.6 (0) (d, *J* = 14.3 Hz), 147.6 (0), 159.0 (0) (d, *J* = 247.4 Hz). HRMS m/z (ESI) calcd for $C_{17}H_{25}OBrFSi$ $(M + H - H_2O)^+$ 371.0844, found 371.0837. Step B: A mixture of 1-(5-bromo-2-fluorophenyl)-4-((tert-butyldimethylsilyl)oxy)-2-methylenebutan-1-ol (923 mg, 2.37 mmol) and manganese dioxide (3.1 g, 35.6 mmol) in chloroform (119 mL) was heated under reflux for 12 h, and then filtered through a pad of Celite. The filtrate was evaporated in vacuo and the residue was purified by silica gel chromatography eluting with 0-5% ethyl acetate//hexanes to give **9b** (706 mg, 77%) as colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 - 7.50 (m, 1H), 7.03 (t, *J* = 8.8 Hz, 1H), 6.10 (s, 1H), 5.78 (d, *J* = 1.5 Hz, 1H), 3.80 (t, J = 6.4 Hz, 2H), 2.68 (td, *J* = 6.3, 0.8 Hz, 2H), 0.90 (s, 9H), 0.07 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (attached protons) -5.4 (2C, 3), 18.3 (0), 25.9 (3C, 3), 34.2 (2), 61.5 (2), 116.6 (0) (d, *J* = 3.6 Hz), 118.0 (1) (d, *J* = 23.3 Hz), 129.1 (0) (d, *J* = 17.1 Hz), 131.1 (2), 132.9 (1) (d, *J* = 3.1 Hz), 135.1 (1) (d, *J* = 8.4 Hz), 145.8 (0), 158.7 (0) (d, *J* = 251.9 Hz), 193,2 (0). HRMS m/z (ESI) calcd for $C_{17}H_{25}O_2BrFSi$ $(M + H)^+$ 387.0792, found 387.0786.

(*R*,*R*)- and (*S*,*S*)-tert-Butyl 7a-(2-fluoro-5-bromophenyl)-4a,5,6,7a-tetrahydro-4H-furo[2,3-d][1,3]thiazin-2-ylcarbamate (7b). To a solution of **9b** (27 g, 69.7 mmol) in acetic acid (225 mL) was added thiourea (15.92 g, 209 mmol) at rt, and the reaction mixture was stirred at rt for 12 h. TBAF (1 M in THF) (105 mL, 105 mmol) was added, and the reaction mixture was heated at 70 °C for 6 h. Acetic acid was removed under reduced pressure, saturated sodium bicarbonate was added, and the aqueous layer was extracted with ethyl acetate (x3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and then filtered. The filtrate was evaporated in vacuo, and the resulting crude product was purified by chiral supercritical fluid chromatography (AD column) to give one enantiomer (A) of 7**b** (5 g, 22% yield) as a white solid and the other enantiomer (B) of 7**b** (4 g, 17% yield) as a white solid. Enantiomer A: retention time: 4.6 min; Enantiomer B: retention time: 7.3 min; (chiral AD-H

250x4.6 mm, CO_2 flow rate: 2.0 mL/min, co-solvent flow rate: 1.0 mL/min, co-solvent: 0.5% Et_2NH in methanol, co-solvent% : 30, total running time: 25 min). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (dd, *J* = 7.0, 2.4 Hz, 1H), 7.37 (ddd, *J* = 8.6, 4.2, 2.7 Hz, 1H), 6.91 (dd, *J* = 11.0, 8.5 Hz, 1H), 4.12 - 3.96 (m, 2H), 3.09 (dd, *J* = 13.1, 4.0 Hz, 1H), 2.93 (ddd, *J* = 12.9, 7.6, 1.8 Hz, 1H), 2.76 - 2.63 (m, 1H), 2.22 - 2.05 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (attached protons) 159.0 (0) (d, *J* = 246.2 Hz), 153.2 (0), 134.0 (0) (d, *J* = 12.2 Hz), 132.4 (1) (d, *J* = 8.6 Hz), 131.2 (1) (d, *J* = 3.4 Hz), 118.3 (1) (d, *J* = 24.1 Hz), 116.7 (0) (d, *J* = 2.1 Hz), 93.3 (0) (d, *J* = 2.5 Hz), 64.7 (2), 37.4 (1), 29.4 (2), and 27.6 (2). Enantiomer A: LCMS m/z: 331.0 $(M + H)^+$. HRMS m/z (ESI) calcd for $C_{12}H_{13}BrFN_2OS$ $(M + H)^+$ 330.9911, found 330.9899. Enantiomer B: LCMS m/z: 331.0 $(M + H)^+$. HRMS m/z (ESI) calcd for $C_{12}H_{13}BrFN_2OS$ $(M + H)^+$ 330.9911, found 330.9900.

1-(3-Bromo-4-fluorophenyl)-4-((tert-butyldimethylsilyl)oxy)-2-methylenebutan-1-one (14). Step A: Step A: To a solution of **10** (3.14 g, 11.82 mmol) in THF (32 mL) at -78 °C was added *tert*-butyllithium (13.9 mL, 23.8 mmol, 1.7 M solution in hexanes) dropwise over a period of 5 min, and the reaction mixture was stirred at -78 °C for 10 min. The resulting lithium reagent was added dropwise to a solution of 3-bromo-4-fluorobenzaldehyde (2 g, 9.8 mmol) in THF (2 mL) at -78 °C, and the reaction mixture was stirred at -78 °C for 30 min. Water was added, the aqueous layer was extracted with ethyl acetate (x3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and then filtered. The filtrate was evaporated in vacuo, and the resulting crude product was purified by silica gel chromatography eluting with 0-5% ethyl acetate//hexanes to give 1-(3-bromo-4-fluorophenyl)-4-(tert-butyldimethylsilyloxy)-2-methylenebutan-1-ol (1.32 g, 34% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 - 7.60 (m, 1H), 7.34 - 7.29 (m, 1H), 7.08 (t, *J* = 8.5 Hz, 1H), 5.19 (d, *J* = 13.6 Hz, 2H), 5.07 (d, *J* = 0.8 Hz, 1H), 4.46 (br. s., 1H), 3.85 - 3.79 (m, 1H), 3.68 (ddd, *J* = 9.7, 7.0, 6.1 Hz, 1H), 2.17 (t, *J* = 5.9 Hz, 2H), 0.94 (s, 9H), 0.12 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (attached protons) -5.5 (2C, 3), 18.4 (0), 25.9 (3C, 3), 34.3 (2), 64.4 (2), 76.0 (1), 108.7 (0) (d, *J* = 21.1 Hz), 115.5 (2), 115.9 (1) (d, *J* = 22.2 Hz), 126.7 (1) (d, *J* = 7.5 Hz), 131.2 (1), 140.5 (0) (d, *J* = 3.3 Hz), 148.9 (0), 158.1 (0, d, *J* = 246.1 Hz). HRMS m/z (ESI) calcd for $C_{17}H_{25}OBrFS_i$ $(M + H - H_2O)^+$ 371.0844, found 371.0837. Step B: A mixture of 1-(3-bromo-4-fluorophenyl)-4-(tert-butyldimethylsilyloxy)-2-methylenebutan-1-ol (1.32 g, 3,39 mmol) and manganese dioxide (4.4 g, 50.9 mmol) in chloroform (113 mL) was heated under reflux for 12 h, and then filtered through a pad of Celite. The filtrate was evaporated in vacuo and the residue was purified by silica gel chromatography eluting with 0-5% ethyl acetate//hexanes to give **14** (1.25 g, 95%) as colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 6.8, 2.0 Hz, 1H), 7.77 (ddd, *J* = 8.4, 4.8, 2.1 Hz, 1H), 7.19 (t, *J* = 8.4 Hz, 1H), 5.94 (d, *J* = 1.0 Hz, 1H), 5.61 (s, 1H), 3.79 (t, *J* = 6.1 Hz, 2H), 2.70 (td, *J* = 6.2, 0.9 Hz, 2H), 0.87 (s, 9H), 0.03 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (attached protons) -5.8 (2C, 3), 17.9 (0), 25.5 (3C, 3), 35.8 (2), 61.2 (2), 108.7 (0) (d, *J* = 21.0 Hz), 115.8 (1) (d, *J* = 23.0 Hz), 130.4 (1) (d, *J* = 9.0 Hz), 134.8 (0) (d, *J* = 8.0 Hz), 135.1 (1), 145.0 (0), 161.1 (0) (d, *J* = 253.0 Hz), and 195.0 (0). HRMS m/z (ESI) calcd for $C_{17}H_{25}O_2BrFS_i$ $(M + H)^+$ 387.0791, found 387.0786.

(4a*SR*,7a*SR*)-7a-(3-Bromo-4-fluorophenyl)-4a,5,6,7a-tetrahydro-4H-furo[*2,3-d*][1,3]thiazin-2-amine (15). To a solution of **14** (1.25 g, 3.23 mmol) in acetic acid (11 mL) was added thiourea (0.73 g, 9.6 mmol) at rt, and the reaction mixture was stirred at rt for 12 h. TBAF (1 M in THF) (4.5 mL, 4.5 mmol) was added, and the reaction mixture was heated at 70 °C for 6 h. Acetic acid was removed under reduced pressure, saturated sodium bicarbonate was added, and the aqueous layer was extracted with ethyl acetate (x3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and then filtered. The filtrate was evaporated in vacuo, and the resulting crude product was purified by preparatibe TLC eluting with 90% DCM/9% MeOH/1% $NH_3 \bullet H_2O$ to give 15 (460 mg, 43% yiled) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.66 (dd, *J* = 6.7, 2.4 Hz, 1H), 7.34 (ddd, *J* = 8.6, 4.7, 2.3 Hz, 1H), 7.09 (t, *J* = 8.4 Hz, 1H), 4.15 - 3.93 (m, 2H), 3.13 (dd, *J* = 13.3, 3.8 Hz, 1H), 2.93 (dd, *J* = 13.3, 5.0 Hz, 1H), 2.38 (tdd, *J* = 8.5, 4.9, 4.0 Hz, 1H), 2.25 (dtd, *J* = 12.4, 8.6, 6.4 Hz, 1H), 2.19 - 2.07 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) (attached protons) δ 158.6 (0) (d, *J* = 246 Hz), 151.9 (0), 141.9 (0) (d, *J* = 3.5 Hz), 131.1 (1), 126.6 (1) (d, *J* = 7.5 Hz), 116.1 (1) (d, *J* = 22.1 Hz), 108.9 (1) (d, *J* = 21.0 Hz), 93.4 (0), 65.3 (2), 38.8 (1), 28.1 (2) and 26.2 (2). LCMS m/z: 332.98 $(M + H)^+$. HRMS m/z (ESI) calcd for $C_{12}H_{13}BrFN_2OS$ $(M + H)^+$ 330.9911, found 330.9900.

5-((tert-Butyldimethylsilyl)oxy)-1-(2,4-difluoro-5-(pyrimidin-5-yl)phenyl)-2-methylenepentan-1-one (16). A solution of ((4-bromopent-4-en-1-yl)oxy)(tert-butyl)dimethylsilane[12] (3.30 g, 11.81 mmol) in THF (25 mL) was added to a flask filled with magnesium (0.574 g, 23.62 mmol) and iodine (0.092 g, 0.363 mmol), and the resulting dark brown suspension was stirred at rt for 15 min and then heated under reflux for 45 min. The color of iodine faded 10 min under reflux, and eventually, the reaction mixture turned to grey. This regent was cooled to rt and then added to a suspension of 2,4-difluoro-5-(pyrimidin-5-yl)benzaldehyde[13] (2 g, 9.08 mmol) in THF (14 mL), and the reaction mixture was stirred at rt for 12 h. Water was added and the aqueous layer was extracted with ethyl acetate (x3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and filtered, and the filtrate was evaporated in vacuo to give the crude product. The crude product was purified by silica gel chromatography eluting with 0-35% ethyl acetate/hexanes to give 5-((tert-butyldimethylsilyl)oxy)-1-(2,4-difluoro-5-(pyrimidin-5-yl)phenyl)-2-methylenepentan-1-ol (1 g, 26 % yield) and **16** (0.95 g, 25 % yield). Treatment of 5-((tert-Butyldimethylsilyl)oxy)-1-(2,4-difluoro-5-(pyrimidin-5-yl)phenyl)-2-methylenepentan-1-ol (1 g, 2.38 mmol) with manganese dioxide (3.1 g, 36 mmol) in chloroform (20 mL) under reflux for 12 h gave **16** (0.83 g, 83% yield). The overall yield of **16** from 2,4-difluoro-5-(pyrimidin-5-yl)benzaldehyde is 47%. ^{1}H NMR (500 MHz, $CDCl_3$) d 9.27 (s, 1H), 8.93 (d, *J* = 1.4 Hz, 2H), 7.59 (dd, *J* = 8.2, 7.5 Hz, 1H), 7.07 (t, *J* = 9.6 Hz, 1H), 6.04 (s, 1H), 5.77 (d, *J* = 2.0 Hz, 1H), 3.70 (t, *J* = 6.3 Hz, 2H), 2.58 - 2.51 (m, 2H), 1.82 - 1.71 (m, 3H), 0.92 (9H, s), and 0.08 (6H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ (attached protons) -5.3 (2C, 3), 18.3 (0), 25.9 (3C, 3), 29.3 (2), 31.3 (2), 62.3 (2), 105.6 (1) (t, *J* = 26.4 Hz), 119.1 (0) (dd, *J* = 3.9, 14.5 Hz), 125.0 (0) (t, *J* = 4.4 Hz), 128.2 (0), 128.7 (2), 131.8 (1) (t, *J* = 4.8 Hz), 148.9 (0), 156.3 (2C, 1), 158.1 (1), 160.6 (0) (dd, *J* = 12.6, 257.7), 161.2 (0) (dd, *J* = 12.6, 257.7 Hz), 193.1 (0). HRMS m/z (ESI) calcd for $C_{22}H_{29}N_2F_2O_2Si$ $(M + H)^+$ 419.1967, found 419.1961.

(4a*SR*,8a*SR*)-8a-(2,4-Difluoro-5-(pyrimidin-5-yl)phenyl)-4,4a,5,6,7,8a-hexahydropyrano[*2,3-d*][1,3]thiazin-2-amine (17). To a solution of **16** (606 mg, 1.45 mmol) in acetic acid (7.3 mL) was added thiourea (441 mg, 5.8 mmol) at rt, and the reaction mixture was stirred at rt for 12 h. TBAF (1 M in THF) (2.2 mL, 2.2 mmol) was added, and the reaction mixture was heated at 70 °C for 6 h. Acetic acid was removed under reduced pressure, saturated sodium bicarbonate was added, and the aqueous layer was extracted with ethyl acetate (x3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and then filtered. The filtrate was evaporated in vacuo, and the resulting crude product was purified by preparatibe TLC eluting with 90% DCM/9% MeOH/1% $NH_3 \bullet H_2O$ to give 15 (170 mg, 34% yiled) as a white solid.. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.22 (s, 1H), 8.91 (d, J = 1.4 Hz, 2H), 7.43 (t, J = 8.5 Hz, 1H), 7.02 (dd, J = 10.8, 10.2 Hz, 1H), 5.0-4.5 (broad s, 2H), 4.00 - 3.92 (m, 1H), 3.88 - 3.80 (m, 1H), 2.95 (dd, J = 12.6, 4.0 Hz, 1H), 2.81 - 2.71 (m, 1H), 2.67 (dd, J = 12.6, 2.8 Hz, 1H), 2.01 - 1.83 (m, 2H), 1.75 - 1.57 (m, 2H). MS 363.03 $(M + H)^+$. ^{13}C NMR (125 MHz, $CDCl_3$): δ (attached protons) 160.4 (0) (dd, J = 11.3, 255 Hz), 159.7 (0) (dd, J = 11.3, 255 Hz), 158.3 (1), 156.0 (2C, 1) (d, J = 3.8 Hz), 153.8 (0), 130.1 (1) (dd, J = 5.0, 10.0 Hz), 128.9 (0) (d, J = 2.5 Hz), 127.8 (0) (dd, J = 3.8, 11.3 Hz), 117.0 (0) (dd, J = 3.8, 8.9 Hz), 106.2 (1) (dd, J = 26.3, 28.8 Hz), 86.3 (0) (d, J = 3.8 Hz), 61.3 (2), 30.5 (1) (d, J = 3.8 Hz), 29.9 (2), 24.9 (2) and 23.5 (2). LCMS m/z: 363.02 $(M + H)^+$. HRMS m/z (ESI) calcd for $C_{17}H_{17}F_2N_4OS$ $(M + H)^+$ 363.1081, found 363.1086.

ASSOCIATED CONTENT

Supporting Information

This supporting information is available free of charge on the ACS Publication website at DOI:.

NMR spectra for all new compounds, analytical chiral HPLC data for **13** and **7b** , and X-ray crystallographic data for (*R*,*R*)-**13** and (*S*,*S*)-**13**.

AUTHOR INFORMATION

Corresponding Author

* Tel: 203-677-7485. E-mail: Yong-jin.wu@bms.com

Notes

The authors declare no competing financial interest.

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