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Stereoselective Synthesis of an Active Metabolite of the Potent PI3 Kinase Inhibitor PKI-179

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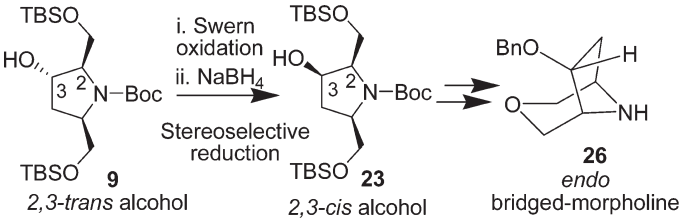

The synthesis and stereochemical determination of 1-(4-(4-((1*R*,5*R*,6*R*)-6-hydroxy-3-oxa-8-azabicyclo[3.2.1]octan-8-yl)-6-morpholino-1,3,5-triazin-2-yl)phenyl)-3-(pyridin-4-yl)urea (**2**), an active metabolite of the potent PI3 kinase inhibitor PKI-179 (**1**), is described. Stereospecific hydroboration of the double bond of 2,5-dihydro-1*H*-pyrrole **8** gave the 2,3-*trans* alcohol **9** exclusively. The configuration of the 3-hydroxyl group in **9** was inverted by an oxidation and stereoselective reduction sequence to give the corresponding 2,3-*cis* isomer **23**. Both *exo* (**21**) and *endo* (**27**) isomers of the metabolite **2** were prepared via a practical synthetic route from **9** and **23**, respectively, and the stereochemistry of **2** was determined to be *endo*. The *endo* isomer (**27**) was separated into two enantiomers **28** and **29** by chiral HPLC. Compound **2** was found to be enantiomerically pure and identical to the enantiomer **28**. The absolute stereochemistry of the enantiomer **28** was determined by Mosher's method, thus establishing the stereochemistry of the active metabolite **2**.

Introduction

A potent PI3Kα/mTOR dual inhibitor, 1-(4-(4-(3-oxa-8-azabicyclo[3.2.1]octan-8-yl)-6-morpholino-1,3,5-triazin-2-yl)-phenyl)-3-(pyridin-4-yl)urea (PKI-179, **1**), is currently being advanced into development for the treatment of solid tumors.[1] In vitro studies showed that **1** was metabolically stable in nude mouse, rat, and dog microsomes, but a major metabolite **2** (Figure 1) was observed when **1** was incubated with human or monkey liver microsomes.[1] Metabolite **2** was isolated and its molecular structure was determined by ^{1}H NMR and LCMS. Biological assays showed that compound **2** is an active metabolite, with in vitro potency comparable to that of the parent compound **1**.[1]

Pharmacologically active metabolites can contribute significantly to the overall therapeutic or adverse effects of drugs.[2] Many active metabolites, such as atorvastatin (Liptor),[3] simavastatin (Zocor),[4] fluoxetine (Prozac),[5] fexofenadine (Allegra),[6] and cetirizine (Zyrtec),[7] have been developed as drugs in their own right. To support further studies of metabolite **2**, including its in vivo, PK, and toxicology, we developed a practical route for the preparation of **2** in gram quantities. We now wish to report on the synthesis of the active metabolite **2** with high stereoselectivity and the determination of its absolute stereochemistry.

Results and Discussion

To assemble the whole molecule of **2**, the 6-hydroxyl bridged-morpholine (**3**) was considered a key building block, because it could be converted to **2** via a route similar to that used for the synthesis of **1**. Since the configuration and

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(1) Mallon, R.; Hollander, I.; Feldberg, L.; Lucas, J.; Soloveva, V.; Gibbons, J.; Venkatesan, A. M.; Chen, Z.; Dos Santos, O.; Dehnhardt, C. M.; Delos Santos, E.; Ayral-Kaloustian, S.; Mansour, T. S. *Cancer Res.* **2009**, in press.

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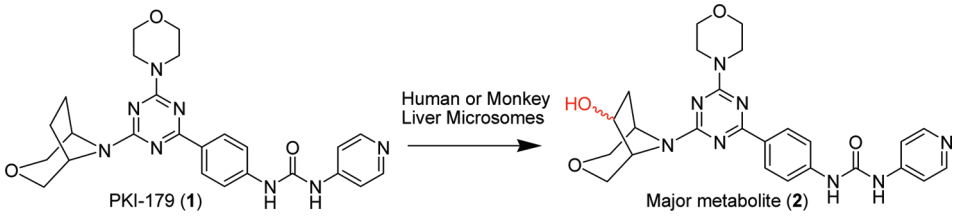
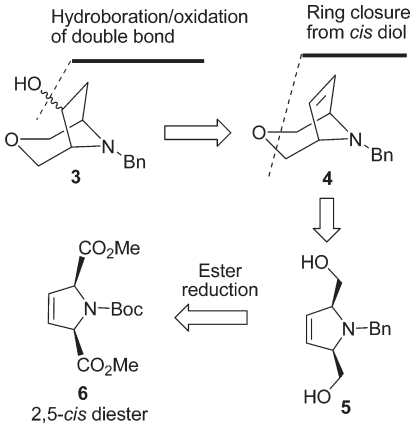


FIGURE 1. Metabolism of PKI-179 (**1**).

SCHEME 1. Retrosynthetic Analysis of the 6-Hydroxy-Bridged Morpholine 3

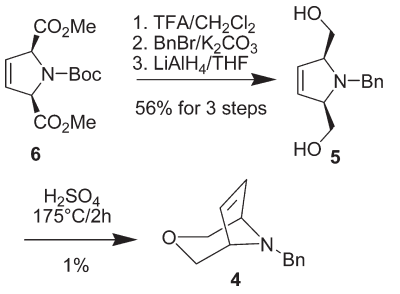


chirality of the hydroxyl group in **2** was not yet determined, we devised a synthetic route to the racemic form of **3**.

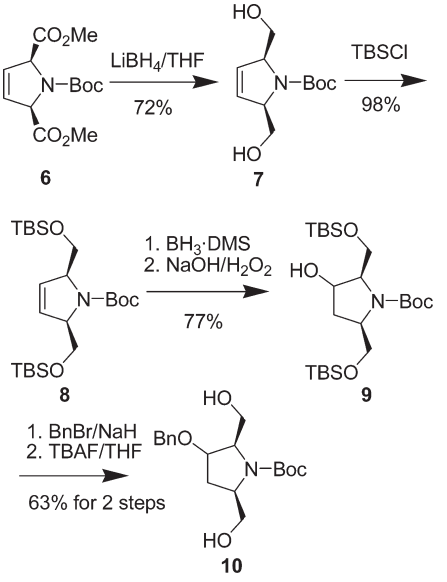
A retrosynthetic analysis of compound **3** (Scheme 1) suggested that *N*-Boc-protected *cis*-2,5-diester **6**, available by a modified Birch reduction under "ammonia-free" conditions,[8] could serve as a starting material. Conversion of the *cis* diester **6** to the corresponding *cis* diol **5** by reduction, followed by ring closure of the *cis* diol **5** could provide the bridged morpholine **4**. Introduction of the hydroxyl group through hydroboration of the double bond in **4** should result in the desired 6-hydroxyl-bridged morpholine **3**.

In our initial approach to the bridged morpholine **4**, following Donohoe's procedure,[9] *cis* diester **6** was prepared in reasonable yield in two steps from *N*-Boc-pyrrole. Conversion of **6** to the corresponding *N*-Bn-protected *cis* diol **5** was achieved by replacement of the Boc group in **6** with a benzyl group followed by reduction with $LiAlH_4$. Heating the *cis* diol **5** with 66% H_2SO_4, followed by basic workup,[10] gave the desired bridged morpholine **4** in low yield (Scheme 2). To improve yield of the cyclization of diol **5** to **4**, we screened a

SCHEME 2



SCHEME 3



variety of known ring-closure methods,[11–16] such as using $SOCl_2$ (1 equiv) in DMF,[11] heating with concd HCl,[12] refluxing with triphenylphosphine in CCl_4,[13] heating with TsCl (3 equiv) in pyridine,[14] or treating with TsCl (1 equiv) in pyridine followed by NaH workup.[15] The desired cyclized product **4** was not under any of these conditions. The observed difficulty of the ring closure for diol **5** may be due to the presence of the double bond in the 5-membered ring, as it has been shown that the saturated analogue of **5** formed the corresponding bicyclic product in high yield under the same conditions.[10]

Manipulation of the double bond in the 5-membered ring prior to ring closure and the synthesis of the advanced diol **10** is shown in Scheme 3. Reduction of the *cis* diester **6** using $LiBH_4$ in THF resulted in the *cis* diol **7** in good yield.

(8) Donohoe, T. J.; Rigby, C. L.; Thomas, R. E.; Nieuwenhuys, W. F.; Bhatti, F. L.; Cowley, A. R.; Bhalay, G.; Linney, I. D. *J. Org. Chem.* **2006**, *71*, 6298–6301.
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(10) Feurer, A.; Flubacher, D.; Weigand, S.; Stasch, J.; Stahl, E.; Schenke, T.; Alonso-alija, C.; Wunder, F.; Lang, D.; Dembowsky, K.; Straub, A.; Perzborn, E. PCT WO 2003/004503.
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(12) Newkome, G. R.; Arai, S.; Gupta, V. K.; Griffin, R. W. *J. Org. Chem.* **1987**, *52*, 5480–5482.
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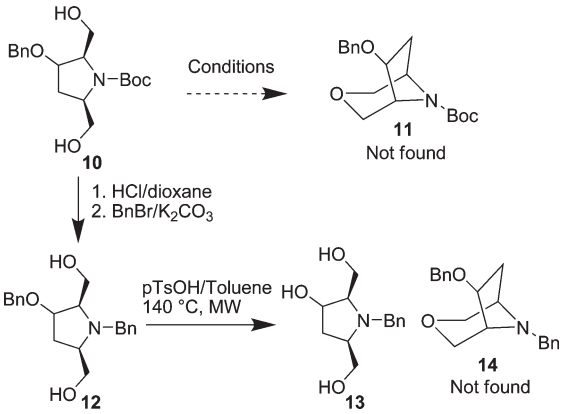
(14) Tadano, K.-I.; Ishihara, J.; Yamada, H.; Ogawa, S. *J. Org. Chem.* **1989**, *54*, 1223–1227.
(15) Barhoumi-Slimi, T.; Crousse, B.; Ourevitch, M.; El Gaied, M.; Begue, J.-P.; Bonnet-Delpon, D. *J. Fluorine Chem.* **2002**, *117*, 137–141.
(16) Huck, B. R.; Gellman, S. H. *J. Org. Chem.* **2005**, *70*, 3353–3362.

SCHEME 4



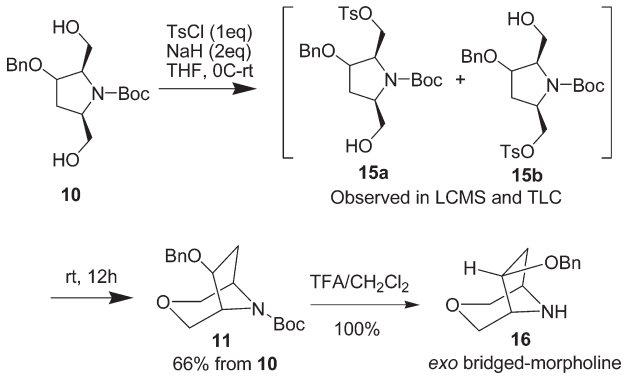
Subsequent protection of both hydroxyl groups with *tert*-butyldimethylsilyl chloride (TBSCl) provided the bis-TBS silyl ether **8**,[16] and introduction of the 3-hydroxyl group was achieved by hydroboration of the double bond using $BH_3 \cdot DMS$, followed by oxidation using H_2O_2/NaOH combination.[17] Benzyl protection of the resulting 3-hydroxyl group of **9**, followed by removal of both TBS protecting groups using TBAF, provided the *cis* diol **10**, which served as a precursor for the ring-closure step.

With the desired diol **10** in hand, we then explored cyclization conditions (Scheme 4). Heating the diol **10** with H_2SO_4 did not yield the desired bicyclic product **11**, and the starting material was destroyed under the harsh conditions. Similarly, no cyclized products were detected under conditions, such as heating with PPh_3/CCl_4.[13] Replacement the *N*-Boc group in **10** with *N*-Bn (an acid-stable group) gave the corresponding diol **12**. The desired ring-closure product **14** was not observed when compound **12** was heated with sulfuric acid or with a catalytic amount of pTsOH in toluene, although a small portion of byproduct **13** was observed under the later conditions.

Treatment of diol **10** with TsCl (1 equiv) in pyridine[15] resulted in recovered starting material without any tosylate formation. However, deprotonation of both hydroxyl groups using NaH (2 equiv) at low temperature, followed by addition of 1 equiv of TsCl, produced the corresponding mixture of monotosylate intermediates **15**. The mixture of tosylates was concentrated to remove the solvent (THF), and the residue was dissolved in DMF and treated with excess KH. The resulting mixture was heated at 100 °C for 30 min under microwave conditions, and the desired bicyclic compound **11** was isolated as a single product in good yield. Through optimization of the reaction conditions, we found that **15** could be completely converted to the cyclized product **11** after stirring overnight at room temperature without the need for microwave irradiation. Removal of the Boc group in **11** using TFA gave the corresponding bridged morpholine **16** in quantitative yield (Scheme 5).

The *exo* configuration of the 6-OBn group in **16** was confirmed by its NMR studies including $^1H-^1H$ COSY, $^1H-^{13}C$ HMBC, and NOE, in particular, the observed NOE correlation between H-6 (δ = 4.36 ppm) and H-4 (δ = 3.83 ppm) as shown in Figure 2. This *exo* selectivity must be

SCHEME 5



derived from its precursor diol **10** with the large 3-OBn group in the *trans* position relative to the 2-CH_2OH group. Hence, the hydroboration of the double bond in **8** must have occurred in a stereoselective manner, exclusively from the less crowded face to form 2,3-*trans* alcohol **9**.

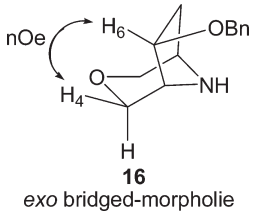


FIGURE 2. Determination of the stereochemistry of the cyclization product **16**. The arrow denotes an observed proton−proton NOE correlation of importance in the *exo*/*endo* determination.

With the *exo* bridged morpholine **16** prepared, the stage was set for the synthesis of the *exo* metabolite **21** (Scheme 6). Compound **17**, readily prepared by reaction of 1 equiv of morpholine with cyanuric chloride, was reacted with **16** at room temperature to give product **18** in good yield. Suzuki coupling of **18** with 4-aminophenylboronic acid pinacol ester under microwave conditions gave aniline **19**, which was converted to 4-pyridylurea **20** by reaction with triphosgene, followed by addition of 4-aminopyridine. Removal of the benzyl group in **20** by catalytic hydrogenation in acidic conditions gave the target compound **21**. Compound **21** displayed the same HRMS and UV spectra as that of the isolated metabolite **2**; however, its ^1H NMR spectrum was not identical to that of **2**. Compounds **2** and **21** were coinjected in HPLC to give two close but distinct peaks. On the basis of these findings, it was clear that the synthetic *exo* isomer **21**, prepared from the *exo* bridged morpholine **16**, was a stereoisomer of the isolated metabolite **2**, suggesting that **2** had an *endo* hydroxyl configuration.

Attempted inversion of the configuration of the hydroxyl group in **21**, using Mitsunobu reaction conditions (PPh_3, DEAD and benzoic acid),[18,19] failed to give the desired *endo* isomer. Tosylation or triflation of the hydroxyl group followed by replacement of the resulting TsO or TfO group

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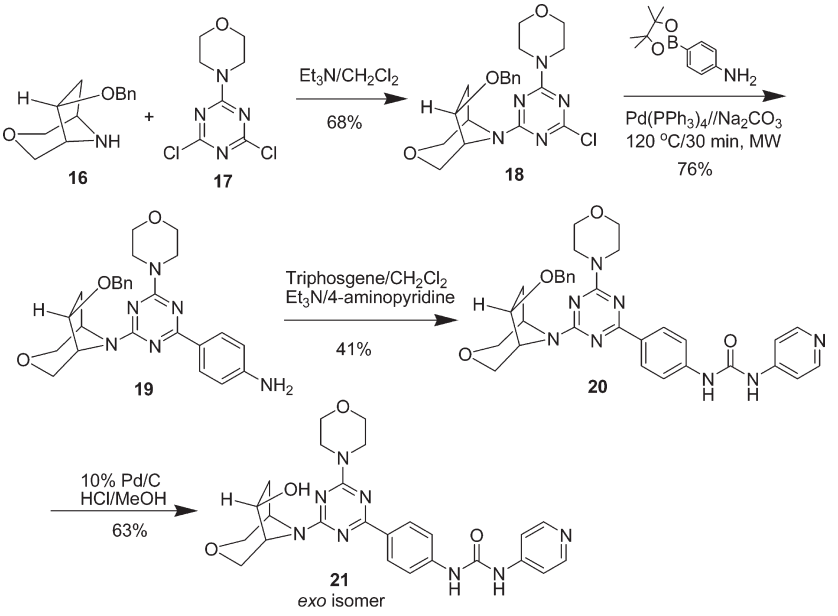
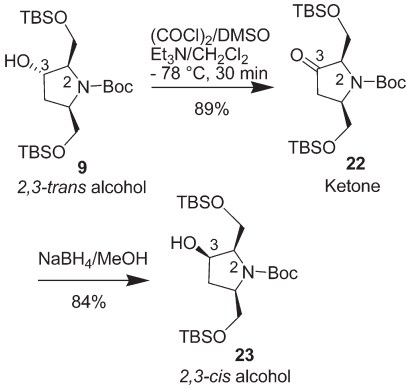
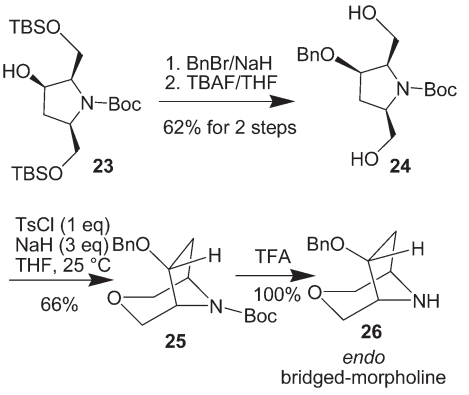
SCHEME 6



SCHEME 7. Conversion of the 2,3-*Trans* Alcohol 9 to the 2,3-*Cis* Alcohol 23



SCHEME 8



using KOAc in DMF[20,21] or KO_2/DMSO[22] failed to yield the desired inversion product. Since attempts to invert the hydroxyl group of **21** were unsuccessful, attention was focused on making the *endo* isomer of the key building block **16**. Mitsunobu reaction of the 2,3-*trans* alcohol **9** failed to give the desired product. Epoxidation of the double bond in **8** using *m*-CPBA[23] gave an inseparable 1:1 mixture of *syn* and *anti* epoxides. Finally, the desired 2,3-*cis* alcohol **23** was readily prepared from the 2,3-*trans* alcohol **9** by Swern oxidation[24] to ketone **22** followed by stereoselctive reduction of the ketone from the *anti* position, using $NaBH_4$, to afford the desired 2,3-*cis* alcohol **23**, exclusively (Scheme 7).

With the desired 2,3-*cis* alcohol **23** in hand, the *endo* bridged-morpholine **26** was prepared in four steps in good yield (Scheme 8). The *endo* configuration of **26** was confirmed by comparing $^1H-^1H$ COSY, $^1H-^1H$ NOE, and $^1H-^{13}C$ HMBC NMR data for **26** to the corresponding data for the *exo* bridged-morpholine **16**.

From the desired *endo* bridged-morpholine **26**, the *endo* isomer **27** was prepared in four steps (26% total yield) by the same synthetic route that was used for the synthesis of the *exo* analogue **21** (Scheme 9).

All the spectral data of the synthetic *endo* isomer **27** (^1H NMR, ^{13}C NMR, HRMS, and LCMS) were found to be identical with those of the isolated metabolite **2**, thus confirming that **2** bears the *endo* hydroxyl configuration (Scheme 10). Therefore, synthesis of the racemic *endo* metabolite **27** was accomplished in 13 steps with 4.3% total yield from the known *cis* diester **6**.

To determine the absolute stereochemistry and enantiomeric purity of **2**, a chiral HPLC method was developed to separate the enantiomers of the synthetic racemic *endo* isomer **27**. The enantiomers **28** and **29** were well separated under chiral HPLC conditions (1:1 ratio), with retention times of 10 and 13.2 min, respectively. Under the same conditions, injection of the isolated sample of metabolite **2**

(20) Kocalka, P.; Pohl, R.; Rejman, D.; Rosenberg, I. *Tetrahedron* **2006**, *62*, 5763–5774.
(21) Shing, T. K.M.; Tai, V. W.-F. *J. Org. Chem.* **1995**, *60*, 5332–5334.
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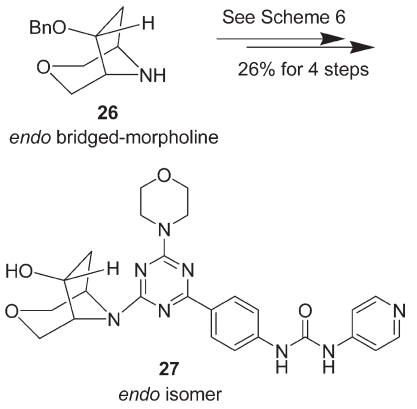
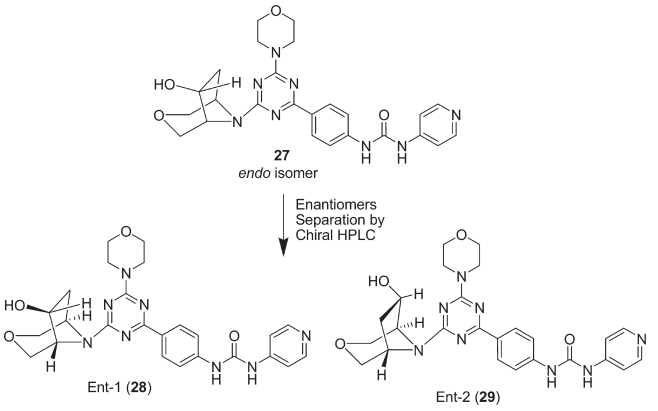
(24) Degnan, A. P.; Meyers, A. I. *J. Org. Chem.* **2000**, *65*, 3503–3512.

SCHEME 9. Synthesis of the *Endo* Isomer 27 from the *Endo*-Bridged Morpholine 26



SCHEME 10



in chiral HPLC gave only one peak with retention time at 10 min, consistent with that of **28**, suggesting that **2** is an enantiomerically pure compound.

The absolute stereochemistry of **28** was determined by Mosher's method. After converting **28** to the (*R*)- and (*S*)-MTPA esters[25] (**28a** and **28b**, respectively) with the corresponding MTPACl, the protons were assigned and their $\Delta\delta$ values ($\delta_S-\delta_R$, ppm) were obtained as shown in Figure 3. Model projection and determination of the configuration of the α center were done according to the empirical method outlined by Kusumi et al.[25] and provided the chirality for C6 and subsequently C1 and C5 which followed from relative stereochemical determination. Combined, these studies indicate that the stereochemistry of **28** should be (1*R*,5*R*,6*R*).

Conclusions

Hydroboration of the double bond in 2,5-dihydro-1*H*-pyrrole **8** gave the 2,3-*trans* alcohol **9** exclusively. Oxidation of the 3-OH group in **9** to the corresponding ketone, was followed by stereospecific reduction by $NaBH_4$ to give the 2,3-*cis* alcohol **23** as the sole product. Both *exo* (**21**) and *endo* (**27**) isomers of the metabolite **2** were prepared via a practical synthetic route from **9** and **23**, respectively, and the stereochemistry of **2** was determined to be *endo*. The enantiomers (**28** and **29**) of the racemic *endo* isomer **27** were separated by chiral HPLC, and **2** was confirmed to be a single enantiomer and identical to the enantiomer **28**. The absolute stereochemistry of **28** (**2**) was determined to be (1*R*,5*R*,6*R*) by Mosher's method. Further studies including in vivo assessment of the active metabolite **2** (**28**) and its PK properties are in progress.

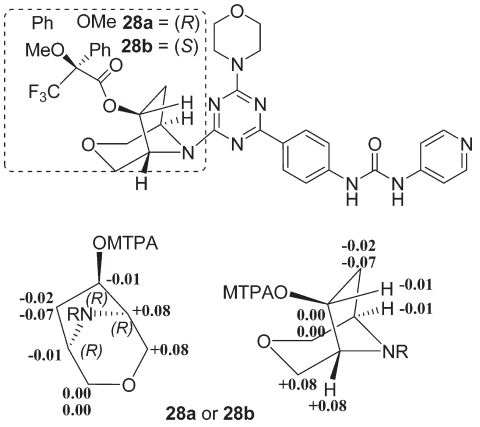


FIGURE 3. $\Delta\delta$ values ($\delta_S-\delta_R$, ppm) for the MTPA esters **28a** and **28b** in ppm (proton NMR spectra measured in DMSO-d_6).

Experimental Section

General Methods. All solvents and reagents were used as received. ^{1}H NMR and ^{13}C NMR spectra were recorded in the solvent indicated at 400 and 100 MHz, respectively. Chemical shifts are reported in parts per million (δ) using tetramethylsilane as the internal standard with coupling constants (*J*) reported in hertz (Hz). The peak shapes are denoted as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; sp, split peak in ^{13}C NMR. Mass spectra (MS) and high-resolution mass spectra (HRMS) were measured with a TOF 2 spectrometer. The purity of final compounds was determined by analytical HPLC. Conditions: ACN/H_2O eluent at 1 mL/min flow (containing 0.05% TFA) at 40 °C, 20 min, gradient 5% ACN to 95% ACN, monitored by UV absorption at 215 nm. All final compounds were found to be ≥95% pure unless otherwise specified. Reversed-phase HPLC purifications were performed on a preparative HPLC system (100 mm × 30 mm column). Thin-layer chromatography (TLC) was performed on TLC silica gel 60F_{254} aluminum sheets and visualized under UV light or developed by immersion in the solution of 20% phosphomolybdic acid in ethanol or in solution of 0.6% $KMnO_4$ and 6% K_2CO_3 in water. Microwave irradiation was performed by using a Biotage Microwave Reactor (model: Initiator EXP60). The terms "concentrated" and "evaporated" refer to removal of solvents using a rotary evaporator at water aspirator pressure with a bath temperature equal to or less than 40 °C.

1-*tert*-Butyl 2,5-dimethyl 1*H*-pyrrole-1,2,5(2*H*,5*H*)-tricarboxylate (**6**, *cis* diester) was synthesized by following the procedure described in the literature:[9] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.97−5.88 (m, 2H), 5.12 (m, 1H), 5.05 (m, 1H), 3.78 (s, 6H), 1.45 (s, 9H); MS (ESI) *m*/*z* 186 (M + H − Boc).

Synthesis of (1-Benzyl-2,5-dihydro-1*H*-pyrrole-2,5-diyl)-dimethanol (5). Step 1. Dimethyl 1-benzyl-2,5-dihydro-1*H*-pyrrole-2,5-dicarboxylate (**6a**, *N*-Bn-protected *cis* diester): To a solution of *cis* diester **6** (2.0 g, 7 mmol) in CH_2Cl_2 (20 mL) was added TFA (4 mL), and the resulting mixture was stirred at room temperature for 2 h. The mixture was concentrated in vacuo to remove as much excess TFA as possible, and the

(25) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096.

residue was dissolved in EtOH (10 mL) and toluene (10 mL). The solvent was removed again, and the residue was dissolved in acetone (10 mL), followed by addition of benzyl bromide (1.66 mL, 14 mmol) and K_2CO_3 (2.9 g, 21 mmol). The mixture was heated in 60 °C for 5 h and cooled to room temperature. The solid was filtered off and washed with acetone, and the resulting filtrate was concentrated to give a residue which was treated with EtOAc and water. The two phases were separated, and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with water and brine and dried ($MgSO_4$). Removal of solvent gave the crude product **6a** (1.92 g, 99%), which was used for next step without purification: MS (ESI) *m*/*z* 276 (M + H).

Step 2. Synthesis of 1-benzyl-2,5-dihydro-1*H*-pyrrole-2,5-diyl)dimethanol (**5**): To a solution of **6a** (1.92 g, 7 mmol) in THF (50 mL) was added slowly $LiAlH_4$ solution (2 M in THF, 10.5 mL, 21 mmol) at 0 °C. The resulting mixture was stirred at rt for 17 h and then cooled to 0 °C again. Water (1 mL) was added dropwise to the reaction mixture, followed by addition of 15% NaOH aqueous solution (1 mL) and water (3 mL). The mixture was stirred at room temperature for 2 h, and the resulting solid was filtered off and washed with THF. The organic solvent was removed in vacuo to give the crude product, which was purified by flash chromatography on silica gel with EtOAc/Hex/MeOH (50:50:5) to give the diol **5** (0.86 g, 57%) as a white solid: mp 67−68 °C (EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35−7.32 (m, 5H), 5.73 (s, 2H), 3.94 (s, 2H), 3.95−3.92 (m, 2H), 3.50 (dd, 2H, J = 10.9, 1.5 Hz), 3.36 (dd, 2H, J = 10.9, 3.0 Hz), 2.46 (br, 2H); MS (ESI) *m*/*z* 220 (M + H); HRMS calcd for $C_{13}H_{17}NO_2$ (M + H) 220.1332, obsd 220.1330.

Synthesis of 8-Benzyl-3-oxa-8-azabicyclo[3.2.1]oct-6-ene (4). A mixture of diol **5** (100 mg, 0.46 mmol) and 66% H_2SO_4 (1.5 mL) was heated at 175 °C for 4 h. The mixture was cooled to room temperature and basified by addition of 5 M NaOH aqueous solution at 0 °C. The mixture was extracted with EtOAc (3 × 50 mL), and the combined organic phases were washed with water and brine and dried ($MgSO_4$). The organic solvent was removed in vacuo, and the residue was purified by flash chromatography on silica gel with EtOAc/Hex (20:80) to give **4** (1 mg, 1%) along with 56 mg of recovered starting material.

Compound **4**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.39−7.28 (m, 5H), 6.13 (s, 2H), 3.76 (d, 2H, J = 9.8 Hz), 3.53 (s, 2H), 3.41 (dd, 2H, J = 12.4, 2.3 Hz); MS (ESI) *m*/*z* 202 (M + H); HRMS calcd for $C_{13}H_{15}NO$ (M + H) 202.1226, obsd 202.1226.

Synthesis of *tert*-Butyl 2,5-Bis(hydroxymethyl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate (7). To a solution of *cis* diester **6** (6.6 g, 23.1 mmol) in THF (100 mL) was added slowly a $LiBH_4$ solution (2 M in THF, 34.7 mL, 69.4 mmol) at 0 °C. The resulting mixture was stirred at rt for 3 h and then cooled to 0 °C again. HCl solution (1 M, 30 mL) was added to the reaction mixture and stirred for 10 min before being diluted with EtOAc. The organic layer was separated, and the aqueous phase was extracted with EtOAc. Combined organic phases were washed with water and brine and dried ($MgSO_4$). The organic solvent was removed in vacuo to give the crude product, which was purified by flash chromatography on silica gel with EtOAc/Hex/MeOH (50:50:10) to give the *cis* diol **7** (3.8 g, 72%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.77 (d, 2H, J = 3.0 Hz), 4.70 (s, 1H), 4.59 (s, 1H), 4.06 (d, 1H, J = 11.3 Hz), 3.97 (d, 1H, J = 11.3 Hz), 3.66 (m, 2H), 1.49 (s, 9H); MS (ESI) *m*/*z* 230 (M + H); HRMS calcd for $C_{11}H_{19}NO_4$ (M + H) 230.1386, obsd 230.1380.

***tert*-Butyl 2,5-Bis((*tert*-butyldimethylsilyloxy)methyl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate (8).** To a solution of diol **7** (3.57 g, 15.6 mmol) in DMF (15 mL) were added TBSCl (5.16 g, 34.3 mmol) and imidazole (3.18 g, 46.7 mmol). The mixture was heated at 80 °C for 30 min in a microwave oven (150 w). Cooled to rt, the mixture was taken up in water (50 mL) and EtOAc (50 mL). The organic layer was separated, and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with water and brine and dried ($MgSO_4$). The organic solvent was removed in vacuo to give the crude product, which was purified by flash chromatography on silica gel with EtOAc/Hex (10:90) to give the **8** (7.12 g, 98%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.85 (d, 2H, J = 3.0 Hz), 4.50 (s, 1H), 4.36 (s, 1H), 3.85 (m, 2H), 3.47 (t, 1H, J = 8.0 Hz), 3.35 (t, 1H, J = 8.7 Hz), 1.43 (s, 9H), 0.85 (s, 9H), 0.84 (s, 9H), 0.00 (s, 12H); MS (ESI) *m*/*z* 458 (M + H); HRMS calcd for $C_{23}H_{47}NO_4Si_2$ (M + H) 458.3116, obsd 458.3118.

Synthesis of *tert*-Butyl 2,5-Bis((*tert*-butyldimethylsilyloxy)methyl)-3-hydroxypyrrolidine-1-carboxylate (9). To a solution of **8** (4.8 g, 10.5 mmol) in THF (50 mL) was added slowly BH_3·DMS solution (2 M in THF, 6.97 mL, 13.9 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 3 h and then cooled to 0 °C again. NaOH solution (5 M, 12.6 mL, 63.2 mmol) was added to the reaction mixture, followed by addition of H_2O_2 (30%, 6.33 mL, 62.0 mmol). The resulting mixture was stirred for 5 h before diluted with EtOAc. The organic layer was separated, and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with water and brine and dried ($MgSO_4$). The organic solvent was removed in vacuo to give the crude product, which was purified by flash chromatography on silica gel with EtOAc/Hex (30:70) to give the **9** (3.8 g, 77%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.35 (s, 1H), 4.0−3.46 (m, 5H), 3.33 (m, 1H), 2.22−2.10 (m, 1H), 1.89−1.73 (m, 1H), 1.39 (s, 9H), 0.82 (s, 18H), −0.01 (s, 6H), −0.03 (s, 6H); MS (ESI) *m*/*z* 476 (M + H); HRMS calcd for $C_{23}H_{49}NO_5Si_2$ (M + H) 476.3222, obsd 476.3218.

Synthesis of *tert*-Butyl 3-(Benzyloxy)-2,5-bis(hydroxymethyl)-pyrrolidine-1-carboxylate (10). Step 1. To a solution of **9** (2.515 g, 5.3 mmol) in THF (50 mL) was added NaH (60%, 0.423 g, 10.6 mmol). The mixture was stirred at rt for 30 min, and benzyl bromide (1.085 g, 6.3 mmol) and TBAI (0.195 g, 0.5 mmol) were added. The mixture was stirred at rt for 12 h and quenched by addition of satd NH_4Cl solution (20 mL). The mixture was concentrated in vacuo, and the residue was taken up in water and EtOAc. The organic layer was separated, and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with water and brine and dried ($MgSO_4$). The organic solvent was removed in vacuo to give the crude product, which was purified by flash chromatography on silica gel with EtOAc/Hex (10:90) to give the 3-OBn intermediate **9a** (3.0 g, 100%) as colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38−7.27 (m, 5H), 4.52 (m, 2H), 4.07 (d, 1H, J = 5.5 Hz), 4.03−3.86 (m, 3H), 3.73−3.55 (m, 2H), 3.45−3.29 (m, 1H), 2.21 (m, 1H), 2.02 (m, 1H), 1.46 (s, 9H), 0.88 (s, 18H), 0.02 (s, 12H); MS (ESI) *m*/*z* 566 (M + H).

Step 2. To a solution of the above intermediate **9a** (3.0 g, 5.3 mmol) in THF (50 mL) was added slowly of TBAF solution (1 M in THF, 21.8 mL, 21.8 mmol) at 0 °C. The resulting mixture was stirred at rt for 6 h and quenched by addition of satd NH_4Cl solution (10 mL). The mixture was concentrated in vacuo, and the residue was treated with water and EtOAc. The organic layer was separated, and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with water and brine and dried ($MgSO_4$). The organic solvent was removed in vacuo to give the crude product, which was purified by flash chromatography on silica gel with EtOAc/Hex/MeOH (50:50:5) to give **10** (1.15 g, 63%): ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.31 (m, 5H), 4.82 (t, 1H, J = 5.5 Hz), 4.71 (s, 1H), 4.47 (m, 2H), 4.02 (s, 1H), 3.89−3.73 (m, 2H), 3.54−3.40 (m, 3H), 3.22 (m, 1H), 2.04 (m, 2H), 1.39 (s, 9H); MS (ESI) *m*/*z* 338 (M + H); HRMS calcd for $C_{18}H_{27}NO_5$ (M + H) 338.1962, obsd 338.1961.

Synthesis of *tert*-Butyl 6-(Benzyloxy)-3-oxa-8-azabicyclo-[3.2.1]octane-8-carboxylate (11). To a solution of diol **10** (1.15 g, 3.4 mmol) in THF (50 mL) was added NaH (60%, 0.409 g,

10.2 mmol). The mixture was stirred at rt for 30 min and cooled to 0 °C. A solution of *p*-TsCl (0.65 g, 3.4 mmol) in THF (5 mL) was slowly added to the mixture. The reaction mixture was then stirred at rt for 12 h and quenched by addition of satd NH_4Cl solution (20 mL). The mixture was concentrated in vacuo, and the residue was taken up with water and EtOAc. The organic layer was separated, and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with water and brine and dried ($MgSO_4$). The organic solvent was removed in vacuo to give the crude product, which was purified by flash chromatography on silica gel with EtOAc/Hex (20:80) to give **11** (716 mg, 66%) as an off-white solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35−7.27 (m, 5H), 4.59−4.43 (m, 2H), 4.38−4.07 (m, 3H), 3.73−3.56 (m, 3H), 3.47 (t, 1H, J = 9.8 Hz), 2.27 (m, 1H), 1.96 (m, 1H), 1.48 (s, 4.5H), 1.44 (s, 4.5H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 153.5 (sp), 138.2, 128.1 (2C), 127.5, 127.4, 127.3, 80.4 (sp), 78.8 (sp), 70.0 (sp), 69.8 (sp), 68.4 (sp), 59.3 (sp), 55.3 (sp), 35.8 (sp), 27.9 (sp, 3C); MS (ESI, m/z) 342 (M + Na); HRMS calcd for $C_{18}H_{25}NO_4$ (M + Na) 342.1676, obsd 342.1670. MS (ESI) m/z 320 (M + H); HRMS calcd for $C_{18}H_{25}NO_4$ (M + H) 320.1857, obsd 320.1856. *The observed split peaks in ^{13}C NMR would be due to the presence of *N*-Boc group, which gives rise to rotamers.

Synthesis of 6-(Benzyloxy)-3-oxa-8-azabicyclo[3.2.1]octane (16). To a solution of **11** (400 mg, 1.2 mmol) in CH_2Cl_2 (10 mL) was added TFA (2 mL). The mixture was stirred at room temperature for 6 h. The mixture was concentrated in vacuo, and the residue was taken up in water and CH_2Cl_2. The mixture was basified by addition of a solution of Na_2CO_3. The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with water and brine and dried ($MgSO_4$). The organic solvent was removed in vacuo to give **16** (275 mg, 100%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37−7.28 (m, 5H), 4.52 (d, 1H, J_{AB} = 11.7 Hz), 4.46 (d, 1H, J_{AB} = 11.7 Hz), 4.33 (dd, 2H, J = 6.8, 2.3 Hz), 3.77−3.60 (m, 4H), 3.49−3.41 (m, 2H), 3.26 (s, 1H), 2.35 (dd, 1H, J = 13.2, 6.8 Hz), 1.81 (m, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 137.6, 128.1 (2C), 127.8 (2C), 127.5, 77.7, 70.3, 67.3, 66.1, 59.4, 55.6, 34.5; MS (ESI) m/z 220 (M + H); HRMS calcd for $C_{13}H_{17}NO_2$ (M + H) 220.1331, obsd 220.1331.

Synthesis of 4-(4,6-Dichloro-1,3,5-triazin-2-yl)morpholine (17). To a solution of cyanuric chloride (51.7 g, 0.28 mol) in CH_2Cl_2 (200 mL) was added dropwise of a solution of morpholine (23.2 g, 0.27 mol) and triethylamine (58.6 mL, 0.42 mol) in CH_2Cl_2 (50 mL) at −78 °C during a period of 2 h. After being stirred for additional 30 min at −78 °C, the reaction mixture was quenched by addition of water (50 mL) and allowed to reach at rt. The organic phase was washed with water three times (100 mL each) and dried over $MgSO_4$. The organic solvent was removed in vacuo to give dichloride **17** (42 g, 64%) as white solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.90 (d, 4H, J = 5.3 Hz), 3.76 (d, 4H, J = 5.3 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 169.1 (2C), 163.4, 65.3 (2C), 44.2 (2C); MS (ESI) m/z 235 (M + H); HRMS calcd for $C_7H_8Cl_2N_4O$ (M + H) 235.0148, obsd 235.0145.

Synthesis of 6-(Benzyloxy)-8-(4-chloro-6-morpholino-1,3,5-triazin-2-yl)-3-oxa-8-azabicyclo[3.2.1]octane (18). To a solution of dichloride **17** (295 mg, 1.3 mmol) in CH_2Cl_2 (10 mL) was added a solution of bridged morpholine **16** (275 mg, 1.3 mmol) and Et_3N (0.5 mL, 3.8 mmol) in CH_2Cl_2 (2 mL) at 0 °C. After being stirred at rt for 3 h, the reaction mixture was diluted with CH_2Cl_2. The organic phase was washed with water and brine and dried over $MgSO_4$. The organic solvent was removed in vacuo to give the crude, which was purified by flash chromatography on silica gel with EtOAc/Hex (30:70) to give **18** (369 mg, 68%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38−7.28 (m, 5H), 4.86 (d, 1/2H, J = 7.5 Hz), 4.80 (d, 1/2H, J = 7.5 Hz), 4.78 (s, 1/2H), 4.60 (s, 1/2H), 4.52 (dd, 2H, J = 11.7, 7.6 Hz), 4.39 (td, 1H, J = 7.1, 2.7 Hz), 3.84−3.62 (m, 11H), 3.55 (d, 1H, J = 13.2 Hz), 2.39 (dd, 1H, J = 13.2, 7.1 Hz), 2.37 (m, 1H); MS (ESI) m/z 418 (M + H); HRMS calcd for $C_{20}H_{24}ClN_5O_3$ (M + H) 418.1640, obsd 418.1646.

Synthesis of 4-(4-(6-(Benzyloxy)-3-oxa-8-azabicyclo[3.2.1]-octan-8-yl)-6-morpholino-1,3,5-triazin-2-yl)aniline (19). To a vial were charged **18** (200 mg, 0.48 mmol), boronic ester (157 mg, 0.7 mmol), $Pd(PPh_3)_4$ (28 mg, 5 mol %), Na_2CO_3 (2M, 1 mL, 2 mmol), and DME (3 mL). The resulting mixture was heated at 120 °C for 60 min in a microwave oven (150 W). Cooled to rt, the mixture was taken up in water and EtOAc. The organic layer was separated, and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with water and brine and dried ($MgSO_4$). The organic solvent was removed in vacuo to give the crude product, which was purified by flash chromatography on silica gel with EtOAc/Hex (50:50) to give the **19** (173 mg, 76%) as yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.22 (d, 2H, J = 8.3 Hz), 7.33−7.21 (m, 5H), 6.67 (d, 2H, J = 8.0 Hz), 5.07 (d, 1/2H, J = 7.2 Hz), 4.97 (s, 1/2H), 4.85 (d, 1/2H, J = 7.6 Hz), 4.70 (s, 1/2H), 4.55 (dd, 2H, J = 18.1, 11.6 Hz), 4.43 (dd, 1H, J = 6.8, 2.3 Hz), 4.01−3.81 (m, 5H), 3.79−3.68 (m, 6H), 2.40 (dd, 1H, J = 13.2, 7.1 Hz), 2.10 (m, 1H); MS (ESI) m/z 475 (M + H); HRMS calcd for $C_{26}H_{30}N_6O_3$ (M + H) 475.2452, obsd 475.2451.

Synthesis of 1-(4-(4-(6-(Benzyloxy)-3-oxa-8-azabicyclo[3.2.1]-octan-8-yl)-6-morpholino-1,3,5-triazin-2-yl)phenyl)-3-(pyridin-4-yl)urea (20). To a solution of triphosgene (91 mg, 0.3 mmol) in CH_2Cl_2 (3 mL) was added a solution of **19** (292 mg, 0.6 mmol) in CH_2Cl_2 (3 mL) at rt, followed by addition of triethylamine (0.26 mL, 1.8 mmol). The mixture was stirred at rt for 15 min, and 4-aminopyridine (290 mg, 3.1 mmol) was added. The mixture was stirred at rt for 6 h and concentrated to give the crude. The crude was subjected to HPLC separation to give **20** (150 mg, 41%) as a white solid: ^{1}H NMR (CD_3OD, 300 MHz) δ 8.37 (m, 4H), 7.58 (m, 4H), 7.34−7.20 (m, 5H), 5.10 (d, 1H, J = 7.1 Hz), 5.01 (s, 1/2H), 4.82 (s, 1/2H), 4.59 (q, 2H, J = 12.1 Hz), 4.47 (d, 1H, J = 6.8 Hz), 3.96−3.56 (m, 12H), 2.43 (m, 1H), 2.00 (m, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 169.1 (sp), 164.6 (sp), 163.9, 151.9, 150.2 (2C), 146.3, 142.3 (sp), 138.2 (sp), 130.4, 129.0 (2C), 128.2, 128.1, 127.9, 127.6, 127.4, 117.5 (2C), 112.3 (2C), 80.6 (sp), 70.1 (sp), 70.0 (sp), 68.5 (sp), 66.0 (2C), 58.6 (sp), 54.6 (sp), 43.2 (2C), 35.9 (sp); MS (ESI) m/z 595 (M + H); HRMS calcd for $C_{32}H_{34}N_8O_4$ (M + H) 595.2775, obsd 595.2764.

Synthesis of 1-(4-(4-(6-Hydroxy-3-oxa-8-azabicyclo[3.2.1]-octan-8-yl)-6-morpholino-1,3,5-triazin-2-yl)phenyl)-3-(pyridin-4-yl)urea (21, *Exo* Isomer). A mixture of **20** (150 mg, 0.25 mmol), Pearlman's catalyst (66 mg), concd HCl (30%, 0.2 mL, 2 mmol), and MeOH (10 mL) was taken for hydrogenation under 50 psi at rt for 12 h. Upon completion, the mixture was filtered through a pad of Celite and washed with MeOH. The resulting filtrate was concentrated in vacuo, and the residue was treated with ether. The resulting white solid was collected by filtration to give **21** (80 mg, 63%): ^{1}H NMR (DMSO-d_6, 600 MHz) δ 9.20 (s, 2H), 8.38 (d, 2H, J = 6.4 Hz), 8.29 (dd, 2H, J = 8.6, 7.1 Hz), 7.57 (d, 2H, J = 8.6 Hz), 7.45 (d, 2H, J = 6.4 Hz), 4.96 (d, 1H, J = 3.7 Hz), 4.93 (d, 1/2H, J = 8.3 Hz), 4.75 (d, 1/2H, J = 7.1 Hz), 4.52 (s, 1/2H), 4.47 (m, 1H), 4.33 (s, 1/2H), 3.90−3.63 (m, 8H), 3.57−3.45 (m, 3H), 2.31 (m, 1H), 1.75 (m, 1H); MS (ESI) m/z 505 (M + H); HRMS calcd for $C_{25}H_{29}N_8O_4$ (M + H) 505.2306, obsd 505.2297.

Synthesis of *tert*-Butyl 2,5-Bis((*tert*-butyldimethylsilyloxy)-methyl)-3-oxopyrrolidine-1-carboxylate (22). To a stirred solution of oxalyl dichloride (2 M in CH_2Cl_2, 10.72 mL, 21.4 mmol) in CH_2Cl_2 (80 mL) was added dropwise DMSO (3.04 mL, 42.9 mmol) at −78 °C. After being stirred for 15 min, a solution of **9** (3.4 g, 7.1 mmol) in CH_2Cl_2 (20 mL) was added dropwise to the reaction mixture. The mixture was stirred at −78 °C for 1 h, and triethylamine (9.96 mL, 71.5 mmol) was added. The mixture was stirred for 5 min before the ice bath was removed, and the

mixture was allowed to reach at rt. The mixture was poured into satd $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined organic phases were washed with water and brine and dried ($MgSO_4$). The organic solvent was removed in vacuo to give the crude product, which was purified by flash chromatography on silica gel with EtOAc/Hex (10:90) to give the ketone **22** (3.02 g, 89%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.24 (s, 1/2H), 4.13 (s, 1/2H), 4.01−3.75 (m, 4H), 3.42 (t, 1H, J = 9.4 Hz), 2.69−2.46 (m, 2H), 1.46 (s, 9H), 0.83 (s, 18H), 0.01 (s, 12H); MS (ESI) m/z 474 (M + H); HRMS calcd for $C_{23}H_{47}NO_5Si_2$ (M + H) 474.3066, obsd 474.3070.

Synthesis of *tert*-Butyl 2,5-bis((*tert*-butyldimethylsilyloxy)-methyl)-3-hydroxypyrrolidine-1-carboxylate (23, 2,3-*Cis* Alcohol). To a solution of ketone **22** (3.02 g, 6.4 mmol) in MeOH (50 mL) was added $NaBH_4$ (0.482 g, 12.8 mmol) in several potions. The mixture was stirred at room temperature for 6 h and quenched by addition of satd NH_4Cl solution (10 mL). The mixture was concentrated in vacuo, and the residue was treated with water and EtOAc. The organic layer was separated, and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with water and brine and dried ($MgSO_4$). The organic solvent was removed in vacuo to give the crude product, which was purified by flash chromatography on silica gel with EtOAc/Hex (10:90) to give the *2,3-cis* alcohol **23** (2.54 g, 84%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.33 (m, 1H), 4.04−3.54 (m, 6H), 2.11 (m, 1H), 2.04−1.95 (m, 1H), 1.40 (s, 9H), 0.84 (s, 18H), 0.03 (s, 6H), 0.02 (s, 6H); MS (ESI) m/z 476 (M + H); HRMS calcd for $C_{23}H_{49}NO_5Si_2$ (M + H) 476.3222, obsd 476.3220.

Synthesis of *tert*-Butyl 3-(benzyloxy)-2,5-bis(hydroxymethyl)-pyrrolidine-1-carboxylate (24). Step 1. To a solution of **23** (2.515 g, 5.3 mmol) in THF (50 mL) was added NaH (60%, 0.423 g, 10.6 mmol). The mixture was stirred at rt for 30 min, and benzyl bromide (1.085 g, 6.3 mmol) and TBAI (0.195 g, 0.5 mmol) were added. The mixture was stirred at rt for 12 h and quenched by addition of satd NH_4Cl solution (20 mL). The mixture was concentrated in vacuo, and the residue was taken up in water and EtOAc. The organic layer was separated, and the aqueous phase was extracted with EtOAc. Combined organic phases were washed with water and brine and dried ($MgSO_4$). The organic solvent was removed in vacuo to give the crude product, which was purified by flash chromatography on silica gel with EtOAc/Hex (10:90) to give **23a** (3.0 g, 100%) as colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40−7.28 (m, 5H), 4.69−4.60 (m, 1H), 4.55 (d, 1H, J = 11.7 Hz), 4.12−3.92 (m, 2H), 3.88−3.66 (m, 5H), 2.13 (m, 2H), 1.47 (s, 9H), 0.88 (s, 18H), 0.02 (s, 12H); MS (ESI) m/z 566 (M + H); HRMS calcd for $C_{30}H_{55}NO_5Si_2$ (M + H) 566.3692, obsd 566.3687.

Step 2. To a solution of **23a** (3.0 g, 5.3 mmol) in THF (50 mL) was added slowly a TBAF solution (1 M in THF, 21.8 mL, 21.8 mmol) at 0 °C. The resulting mixture was stirred at rt for 6 h and quenched by addition of satd NH_4Cl solution (10 mL). The mixture was concentrated in vacuo, and the residue was treated with water and EtOAc. The organic layer was separated, and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with water and brine and dried ($MgSO_4$). The organic solvent was removed in vacuo to give the crude product, which was purified by flash chromatography on silica gel with EtOAc/Hex/MeOH (50:50:5) to give **24** (1.15 g, 62%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.39−7.27 (m, 5H), 4.63 (d, 1H, J_{AB} = 11.7 Hz), 4.50 (d, 1H, J_{AB} = 11.7 Hz), 4.18 (m, 1H), 4.04 (br, 1H), 3.98−3.70 (m, 4H), 3.61 (dd, 1H, J = 11.7, 5.7 Hz), 2.37−2.13 (m, 1H), 1.85 (br, 1H), 1.47 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 136.1, 128.6 (2C), 128. 1, 127.7 (2C), 81.1, 77.2, 72.1, 66.9, 62.2, 60.4, 58.5, 32.2, 28.4 (3C); MS (ESI) m/z 338 (M + H); HRMS calcd for $C_{18}H_{27}NO_5$ (M + Na) 360.1781, obsd 360.1779.

Synthesis of *tert*-Butyl 6-(benzyloxy)-3-oxa-8-azabicyclo-[3.2.1]octane-8-carboxylate (25). To a solution of diol **24** (1.15 g, 3.4 mmol) in THF (50 mL) was added NaH (60%, 0.409 g, 10.2 mmol). The mixture was stirred at room temperature for 30 min and cooled down to 0 °C. A solution of *p*-TsCl (0.65 g, 3.4 mmol) in THF (5 mL) was slowly added to the mixture. The reaction mixture was then stirred at room temperature for 12 h and quenched by addition of satd NH_4Cl solution (20 mL). The mixture was concentrated in vacuo, and the residue was taken up in water and EtOAc. The organic layer was separated, and the aqueous phase was extracted with EtOAc. Combined organic phases were washed with water and brine and dried ($MgSO_4$). The organic solvent was removed to give the crude product, which was purified by flash chromatography on silica gel with EtOAc/Hex (20:80) to give **25** (716 mg, 66%) as an off-white solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.39−7.27 (m, 5H), 4.67−4.54 (m, 2H), 4.17−3.87 (m, 4H), 3.82−3.62 (m, 2H), 3.58 (d, 1H, J = 11.0 Hz), 2.39 (m, 1H), 1.88 (dd, 1H, J = 12.8, 4.2 Hz), 1.46 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.5, 138.0, 128.4 (2C), 127.7 (3C), 80.1, 77.2, 72.3, 70.8, 66.1, 56.2 (sp), 54.3 (sp), 33.7 (sp), 28.4 (3C); MS (ESI) m/z 342 (M + Na); HRMS calcd for $C_{18}H_{25}NO_4$ (M + Na) 342.1676, obsd 342.1676.

Synthesis of 6-(Benzyloxy)-3-oxa-8-azabicyclo[3.2.1]octane (26, *Endo*-Bridged Morpholine). To a solution of **25** (716 mg, 2.2 mmol) in CH_2Cl_2 (10 mL) was added TFA (2 mL). The mixture was stirred at room temperature for 6 h. The mixture was diluted with CH_2Cl_2 and basified by addition of a solution of Na_2CO_3. The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with water and brine and dried ($MgSO_4$). The organic solvent was removed in vacuo to give the product *endo*-bridged morpholine **26** (492 mg, 100%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.39−7.27 (m, 5H), 4.68 (d, 1H, J_{AB} = 11.7 Hz), 4.56 (d, 1H, J_{AB} = 11.7 Hz), 4.43 (m, 1H), 4.15−3.96 (m, 3H), 3.68 (d, 2H, J = 9.8 Hz), 3.53 (d, 1H, J = 6.0 Hz), 2.58−2.48 (m, 1H), 2.0 (dd, 1H, J = 13.6, 4.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.7, 128.5 (2C), 127.9, 127.8 (2C), 77.3, 72.9, 70.7, 65.9, 56.4, 54.8, 32.8; MS (ESI) m/z 220 (M + H); HRMS calcd for $C_{13}H_{17}NO_2$ (M + H) 220.1332, obsd 220.1329.

Synthesis of 1-(4-(4-(6-Hydroxy-3-oxa-8-azabicyclo[3.2.1]-octan-8-yl)-6-morpholino-1,3,5-triazin-2-yl)phenyl)-3-(pyridin-4-yl)urea (27, *Endo* Isomer). Step 1. Synthesis of 6-(benzyloxy)-8-(4-chloro-6-morpholino-1,3,5-triazin-2-yl)-3-oxa-8-azabicyclo[3.2.1]octane (**26a**, *endo*): To a solution of dichloride **17** (1.055 g, 4.5 mmol) in CH_2Cl_2 (50 mL) was added a solution of *endo*-bridged morpholine **26** (0.492 g, 2.2 mmol) and Hunig's base (1.2 mL, 6.7 mmol) in CH_2Cl_2 (5 mL) at 0 °C. After being stirred at rt for 3 h, the reaction mixture was diluted with CH_2Cl_2. The organic phase was washed with water and brine and dried over $MgSO_4$. The organic solvent was removed in vacuo to give the crude, which was purified by flash chromatography on silica gel with EtOAc/Hex (30:70) to give **26a** (856 mg, 91%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40−7.28 (m, 5H), 4.72−4.43 (m, 4H), 4.16 (m, 1H), 4.10 (d, 1H, J = 10.9 Hz), 3.86−3.63 (m, 11H), 2.42 (m, 1H), 2.0 (dd, 1H, J = 12.8, 4.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.8, 164.4, 162.5, 137.9, 128.5 (2C), 127.8, 127.7, 127.6, 76.4, 72.3 (sp), 70.9 (sp), 66.5 (2C), 65.9, 55.9 (sp), 54.0 (sp), 43.8 (2C), 33.4; MS (ESI) m/z 418 (M + H); HRMS calcd for $C_{20}H_{24}ClN_5O_3$ (M + H) 418.1640, obsd 418.1638.

Step 2. Synthesis of 4-(4-(6-(benzyloxy)-3-oxa-8-azabicyclo-[3.2.1]octan-8-yl)-6-morpholino-1,3,5-triazin-2-yl)aniline (**26b**, *endo*): To a vial were charged with **26a** (856 mg, 2.0 mmol), boronic ester (673 mg, 3.1 mmol), $Pd(PPh_3)_4$ (118 mg, 0.1 mmol), Na_2CO_3 (2M, 4.1 mL, 8.2 mmol), and DME (8 mL). The resulting mixture was heated at 120 °C for 30 min in a microwave oven (150 w). Cooled to rt, the mixture was taken up in water and EtOAc. The organic layer was separated, and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with water and brine and dried ($MgSO_4$). The organic solvent was removed in vacuo to give the crude product,

which was purified by flash chromatography on silica gel with EtOAc/Hex (50:50) to give the **26b** (800 mg, 82%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.18 (d, 2H, J = 8.6 Hz), 7.43−7.28 (m, 5H), 6.68 (d, 2H, J = 8.7 Hz), 4.86−4.51 (m, 4H), 4.20 (m, 1H), 4.10 (d, 1H, J = 10.6 Hz), 3.98−3.61 (m, 13H), 2.46 (m, 1H), 2.01 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.4, 165.2, 164.0, 149.6, 138.2, 130.0 (2C), 128.4 (2C), 127.7 (3C), 127.1, 114.1 (2C), 77.2, 72.3, 70.6 (sp), 66.8 (2C), 65.9 (sp), 55.7 (sp), 53.7 (sp), 43.6 (2C), 33.6; MS (ESI) m/z 475 (M + H); HRMS calcd for $C_{26}H_{30}N_6O_3$ (M + H) 475.2452, obsd 475.2448.

Step 3. Synthesis of 1-(4-(4-(6-(benzyloxy)-3-oxa-8-azabicyclo[3.2.1]octan-8-yl)-6-morpholino-1,3,5-triazin-2-yl)phenyl)-3-(pyridin-4-yl)urea (**26c**, *endo*): To a solution of triphosgene (144 mg, 0.5 mmol) in CH_2Cl_2 (5 mL) was added a solution of **26b** (385 mg, 0.8 mmol) in CH_2Cl_2 (3 mL) at rt, followed by addition of triethylamine (0.11 mL, 0.8 mmol). The mixture was stirred at rt for 15 min, and 4-aminopyridine (382 mg, 4.1 mmol) was added, followed by addition of triethylamine (0.22 mL, 1.6 mmol). The mixture was stirred at rt for 6 h and concentrated to give the crude. The crude was subjected to HPLC separation to give **26c** (288 mg, 60%) as a white solid: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.20 (s, 1H), 9.18 (s, 1H), 8.38 (d, 2H, J = 6.5 Hz), 8.29 (d, 2H, J = 7.9 Hz), 7.57 (d, 2H, J = 9.4 Hz), 7.45 (d, 2H, J = 6.1 Hz), 7.43−7.28 (m, 5H), 4.78 (m, 1H), 4.61 (m, 2H), 4.18 (m, 1H), 4.0−3.55 (m, 13H), 2.43 (m, 1H), 1.86 (d, 1H, J = 12.5 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 169.2, 164.6, 163.3, 151.9, 150.2 (2C), 146.2, 142.3, 138.4, 130.3, 129.1, 128.2 (2C), 127.7 (2C), 127.5 (2C), 117.5 (2C), 112.3 (2C), 76.7, 71.2 (2C), 66.0 (2C), 65.0, 55.1 (2C), 43.2 (2C), 33.0; MS (ESI) m/z 595 (M + H); HRMS calcd for $C_{32}H_{34}N_8O_4$ (M + H) 595.2775, obsd 595.2768.

Step 4. Synthesis of 1-(4-(4-(6-hydroxy-3-oxa-8-azabicyclo-[3.2.1]octan-8-yl)-6-morpholino-1,3,5-triazin-2-yl)phenyl)-3-(pyridin-4-yl)urea (**27**, *endo* isomer): A mixture of **26c** (288 mg, 0.5 mmol), 10% Pd/C (188 mg), concd HCl (30%, 0.5 mL, 4.9 mmol), and MeOH (20 mL) was hydrogenated under 50 psi at rt for 24 h. Upon completion, the mixture was filtered through a pad of Celite and washed with MeOH. The resulting filtrate was concentrated in vacuo, and the residue was treated with ether. The resulting white solid was collected by filtration to give **27** (HCl salt, 150 mg, 57%): mp 195−198 °C (MeOH); HPLC purity 96.4%; ^{1}H NMR (DMSO-d_6, 600 MHz) δ 11.05 (s, 1H), 10.25 (s, 1H), 8.63 (d, 2H, J = 7.0 Hz), 8.31 (t, 2H, J = 8.4 Hz), 7.97 (d, 2H, J = 6.3 Hz), 7.64 (d, 2H, J = 8.8 Hz), 4.74 (d, 1/2H, J = 7.4 Hz), 4.55 (d, 1/2H, J = 7.3 Hz), 4.52 (d, 1/2H, J = 5.8 Hz), 4.34 (d, 1/2H, J = 5.9 Hz), 4.29 (m, 1H), 4.01 (dd, 1H, J = 16.8, 11.0 Hz), 3.95−3.55 (m, 11H), 2.39 (m, 1H), 1.72 (m, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 168.7, 164.4, 162.8, 153.8, 151.2, 141.8 (2C), 141.5, 130.9 (sp), 129.2 (2C), 118.0 (2C), 113.0 (2C), 70.1 (sp), 68.9 (sp), 66.0 (2C), 65.1 (sp), 57.0 (sp), 53.7 (sp), 43.3 (2C), 35.3 (sp); MS (ESI) m/z 505 (M + H); HRMS calcd for $C_{25}H_{28}N_8O_4$ (M + H) 505.2306, obsd 505.2300.

Separation of Racemic *Endo* Isomer 27 by Chiral HPLC To Give Enantiomers 28 and 29. Separation conditions: column: Chiralpak IA 250 × 4.6 mm; mobile phase: 70% heptane/DEA 30% ethanol; flow: 1.0 mL/min; column temperature: 40°C; UV wavelength: 215 and 254 nm; retention time: 10.4 min for ent-1 (**28**) and 13.6 min for ent-2 (**29**).

The *endo* isomer **27** (100 mg) was subjected to chiral HPLC separation under the above conditions to give enantiomers **28** (27 mg) and **29** (24 mg) and a mixture (35 mg) containing both **28** and **29**.

1-(4-(4-((1*R*,5*R*,6*R*)-6-Hydroxy-3-oxa-8-azabicyclo[3.2.1]octan-8-yl)-6-morpholino-1,3,5-triazin-2-yl)phenyl)-3-(pyridin-4-yl)-urea (**28**, identical with the metabolite **2**): HPLC purity 98.0%; chiral purity 96.0% ee; $[\alpha]^{25}_D$ = −7.5 (DMSO, 1%); ^{1}H NMR (DMSO-d_6, 600 MHz) δ 9.23 (s, 1H), 9.22 (s, 1H), 8.37 (d, 2H, J = 6.6 Hz), 8.27 (t, 2H, J = 7.7 Hz), 7.56 (d, 2H, J = 8.8 Hz), 7.45 (d, 2H, J = 6.6 Hz), 5.17 (br, 1H), 4.73 (d, 1/2H, J = 7.3 Hz), 4.54 (d, 1/2H, J = 7.3 Hz), 4.51 (d, 1/2H, J = 5.5 Hz), 4.33 (d, 1/2H, J = 5.5 Hz), 4.28 (m, 1H), 4.0 (dd, 1H, J = 18.7, 11.0 Hz), 3.90−3.54 (m, 11H), 2.39 (m, 1H), 1.72 (m, 1H); MS (ESI) m/z 505 (M + H); HRMS calcd for $C_{25}H_{28}N_8O_4$ (M + H) 505.2306, obsd 505.2313.

1-(4-(4-((1*S*,5*S*,6*S*)-6-Hydroxy-3-oxa-8-azabicyclo[3.2.1]octan-8-yl)-6-morpholino-1,3,5-triazin-2-yl)phenyl)-3-(pyridin-4-yl)urea (**29**): HPLC purity 97.8%; chiral purity 97.8% ee; ^{1}H NMR (DMSO-d_6, 600 MHz) δ 9.18 (s, 1H), 9.16 (s, 1H), 8.37 (d, 2H, J = 6.6 Hz), 8.27 (t, 2H, J = 7.7 Hz), 7.56 (d, 2H, J = 8.8 Hz), 7.45 (d, 2H, J = 6.6 Hz), 5.17 (br, 1H), 4.73 (d, 1/2H, J = 7.3 Hz), 4.54 (d, 1/2H, J = 7.0 Hz), 4.51 (d, 1/2H, J = 5.5 Hz), 4.33 (d, 1/2H, J = 5.9 Hz), 4.28 (br, 1H), 4.0 (dd, 1H, J = 18.7, 10.6 Hz), 3.90−3.54 (m, 11H), 2.39 (m, 1H), 1.72 (m, 1H); MS (ESI) m/z 505 (M + H); HRMS calcd for $C_{25}H_{28}N_8O_4$ (M + H) 505.2306, obsd 505.2315.

Preparation of (*R*)- and (*S*)-MTPA Esters 28a and 28b.[25] To a suspension of **28** (3 mg, 5.95 μmol) in CH_2Cl_2 (0.5 mL) was added pyridine (5 μL, 0.06 mmol) to form a solution. The mixture was cooled to 0 °C, and (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl chloride (3 mg, 0.012 mmol) was added, followed by DMAP (0.8 mg, 5.95 μmol). The mixture was stirred at 0 °C for 5 h and concentrated to remove the solvent, and the residue was subjected to HPLC separation to give (*R*)-MTPA ester (**28a**) as a white solid (2.6 mg, 61%).

(*S*)-MTPA ester (**28b**) was prepared by the method used for the preparation of **28a** by using (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl chloride to give a white solid (1.5 mg, 35%). For the proton chemical shifts and NMR assignments for both **28a** and **28b**, see Table S1 in the Supporting Information.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of most of the reported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.