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Stereochemistry as a Tool in Deciphering the Processes of a Tandem Iminium Cyclization and Smiles Rearrangement

Jinbao Xiang, Tong Zhu, Qun Dang,* and Xu Bai*

The Center for Combinatorial Chemistry and Drug Discovery, The School of Pharmaceutical Sciences and The College of Chemistry, Jilin University, 1266 Fujin Road, Changchun, Jilin 130021, P. R. China

xbai@jlu.edu.cn; qdang@jlu.edu.cn

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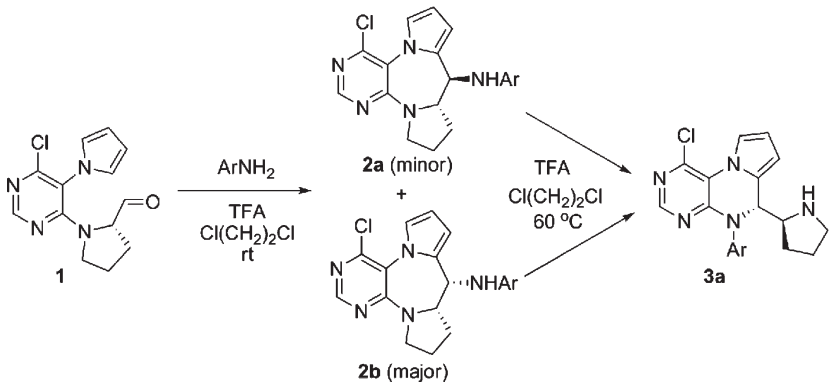

To understand the detailed mechanism of a recently reported tandem iminium cyclization and Smiles rearrangement, the reaction processes of a chiral substrate were investigated by monitoring its stereochemical courses. Under the tandem reaction conditions, chiral aldehyde **1** derived from L-prolinol led to two surprising results. First, the iminium cyclization gave a diastereomeric mixture with the *cis*-configured product as the predominant one. Second, Smiles rearrangement of both *cis*- and *trans*-**2** led to the same product **3a** directly derived from the *trans* isomer. The former was rationalized by the postulation of a Cram's chelate transition state leading to the *cis* product as kinetically favored. The latter was due to the equilibration between the *trans*/*cis* pair involving a carbocation intermediate and the steric hindrance, which prevented the *cis* isomer from undergoing the intramolecular nucleophilic substitution. This hypothesis was further supported by the results of a competition experiment in which the addition of 1 equiv of *p*-methoxyaniline in the rearrangement step led to a significant amount of anilinyl-exchanged rearrangement product.

Introduction

Mechanistic studies have been an important area of organic chemistry research[1−3] which can provide insights to reaction processes and facilitate the design of the next generation of reactions that may be more efficient or stereospecific.[2] Stereochemistry has often been used as a powerful tool in elucidation of reaction processes.[3]

Recently, we reported a new tandem reaction entailing an iminium cyclization followed by a Smiles rearrangement in a *N*-pyrrolopyrimidine and analogous systems.[4] As depicted in Scheme 1, the reaction of aldehyde **A** with a primary amine yields an *exo* iminium cyclization product diazepine **B** under acidic conditions; subsequently, diazepine **B** may undergo an

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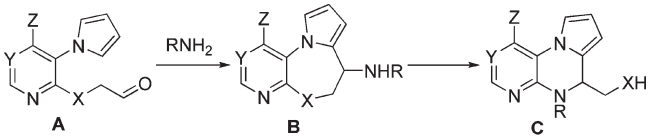
SCHEME 1. Tandem Iminium Cyclization and Smiles Rearrangement



intramolecular nucleophilic displacement (Smiles rearrangement) to produce pteridine derivative **C**. To the best of our knowledge, this is the first reported cascade of reactions consisting of both electrophilic cyclization and nucleophilic substitution in a single molecular system. Although a plausible mechanism was proposed for this reaction in our initial disclosure,[4b] details of the reaction processes remained to be investigated. Thus, further investigation of the reaction mechanism is warranted. A molecular system with a stereogenic center next to the reaction centers in the substrate, was designed to the study of the tandem reaction process. Herein, the results of the investigations and rationalizations are presented.

Results and Discussion

Design of the Molecular System. To study the stereochemical transformations of the current tandem reaction, chiral substrate **1** derived from L-prolinol was designed (Scheme 2). Theoretically, aldehyde **1**, without racemization, reacts with an amine to give either *trans*-diazepine **2a** (path a) or *cis*-**2b** (path b) (via an imine intermediate),[3a,5] subsequent Smiles rearrangement of *trans*-diazepine **2a** and *cis*-**2b** should form epimers **3a** and **3b**, respectively, in an S_N2 process. On the other hand, racemization at either the iminium cyclization step and/or Smiles rearrangement step would lead to more complicated stereochemical outcomes in this tandem reaction. Therefore, investigation of the stereochemical transitions in this molecular system should reveal insights to the reaction processes.

The Iminium Cyclization of Chiral Aldehyde 1 to Diazepines 2. Aldehyde **1** was readily prepared according to Scheme 3. Substitution of 4,6-dichloro-5-(1*H*-pyrrol-1-yl)-pyrimidine **4**[4a] with L-prolinol produced intermediate **5** in high yield, and subsequent Parikh−Doering oxidation of alcohol **5** provided aldehyde **1**.[6] Attempted isolation of aldehyde **1** using silica gel column led to hydroxydiazepines **6** resultimg from an intramolecular attack of the aldehyde by the pyrrolyl group,[4a,7] presumably promoted by the slightly acidic silica gel. Therefore, the crude aldehyde **1** was used immediately for the iminium cyclization reaction without further purification.

The cyclization reactions of aldehyde **1** with several anilines under conditions of trifluoroacetic acid−dichloroethane (TFA−$Cl(CH_2)_2Cl$) at ambient temperature were investigated, and the results are summarized in Table 1. In general, the iminium cyclizations proceeded in good to excellent yields and with the *cis* cyclization product being preferentially produced in most cases. The selectivity for *cis* products are more pronounced with electron-rich anilines (entry 1, Table 1) compared to electron-deficient anilines (entries 4 and 5, Table 1). It is interesting to note that 24% of the direct aldehyde cyclization product **6** was isolated when *p*-nitroaniline was used, which indicated that the imine formation reaction is much slower for the electron-deficient aniline. The chiral aldehyde **1** was then subjected to the current reaction conditions without an aniline present, which produced the hydroxydiazepines **6** in excellent yield (entry 6, Table 1). Moreover, the cyclization of aldehyde **1** was much more stereoselective than imine cyclization (entry 6 vs entries 1−5, Table 1).

The acid-catalyzed ring closure reactions may be rationalized by a combination of steric and electronic effects in the two competing transition-state conformations as shown in Figure 1. First, the pyrimidine (A) and pyrrole (B) rings are likely to be nonplanar.[8] Second, the π-orbitals of the B ring should be periplanar to the ones of the reacting double bond (carbonyl or iminium) in order to form a σ bond (cyclization).[9] Third, the approach of B ring to the double bond should come from the less hindered H-atom side of the pyrolidine ring (C). Therefore, the approaching direction of B ring to the double bond was dictated by the configuration of the stereogenic carbon in the C ring, and the orientation of the double bond (iminium or carbonyl) could determine the formation of the *trans* (*Re*-face attacked) cyclized product or *cis* (*Si*-face attacked) one. It is postulated that the formation of a cyclic transition state via intramolecular hydrogen bond between the pyrrolidinyl nitrogen and the proton of either protonated imine or aldehyde[10] made the *Si*-face attack (Figure 1, chelate mode) kinetically favored following Cram's rule over the *Re*-face attack (Figure 1, open mode). These rationalizations are consistent with the experimental results. There is less steric hindrance within the cyclic transition state (via hydrogen bond) for the aldehyde over an imine, which explains why the cyclization of aldehyde is more stereoselective than the imine.

Do Diazepines 2 Come from Hydroxydiazepines 6 or Imine Intermediate 7? The ease of self-cyclization of aldehyde **1** raised the question how diazepines **2** were formed. For example, diazeines **2.4** could be formed from the direct cyclization of the imine intermediate **7.4** or they could be produced from the nucleophilic substitution of alcohol **6** by *p*-chloroaniline (Scheme 4). Thus, hydroxydiazepines **6** were

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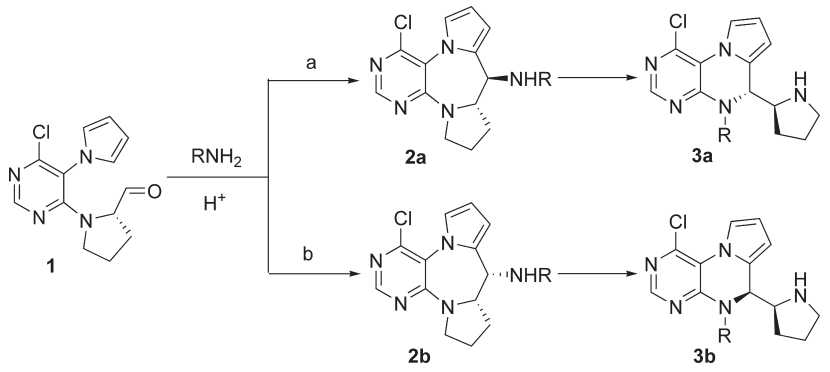
SCHEME 2. Possible Stereochemical Paths in Tandem Iminium Cyclization and Smiles Rearrangement



SCHEME 3. Preparation of Chiral Aldehyde 1

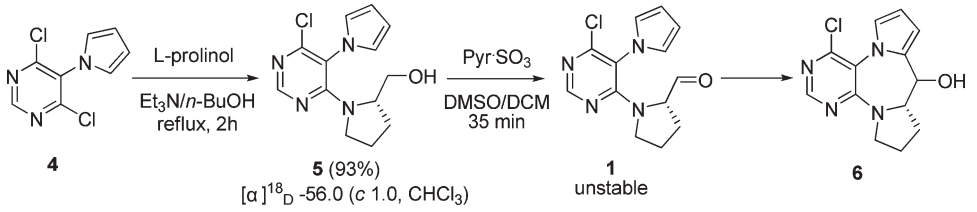


TABLE 1. Cyclization Results (Schemes 2 and 3)

entry	RNH_2	**2** or **6**	yield (%)	*trans*/*cis*
1	*p*-$MeOPhNH_2$	**2.1**	83	1:9.1
2	*p*-$MePhNH_2$	**2.2**	85	1:3.7
3	$PhNH_2$	**2.3**	80	1:3.2
4	*p*-$ClPhNH_2$	**2.4**	86	1:2.1
5	*p*-NO_2PhNH_2	**2.5**	69[a]	1:1.0
6		**6**	86	1:28

[a]24% hydroxydiazepine **6** was also isolated.

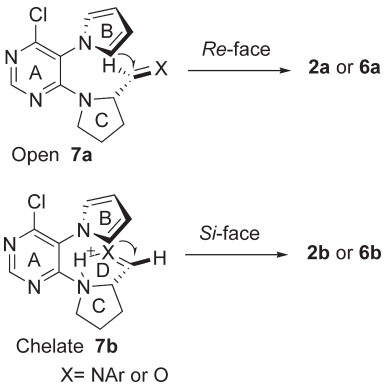


FIGURE 1. Transition-state conformations of the cyclization reaction.

treated with *p*-chloroaniline for 10 min in $TFA/Cl(CH_2)_2Cl$ at room temperature (the exact cyclization condition), but no diazepines **2.4** were observed, and instead 97% of compound **6** was recovered. Therefore, the results confirmed that diazepines **2.4** were indeed produced via direct cyclization of imine **7.4**, not amine substitution of the hydroxyl group in **6** (Scheme 4).

Determination of the Absolute Configurations of Diazepines 2.4. A pure sample of the major product **2.4b** was obtained by recrystallization, while the minor product **2.4a** was purified by flash chromatography. The structure of product **2.4b** was unambiguously determined as the *cis* configuration in the diazepine ring by an X-ray diffraction analysis (Figure S-18, Supporting Information).

Study of the Smiles Rearrangement. If the Smiles rearrangement follows the direct S_N2 process, compounds **2.4a** and **2.4b** should yield products **3.4a** and **3.4b**, respectively (Scheme 2). However, it is interesting to note that both **2.4a** and **2.4b** were converted to the same product **3.4a** (small amount of an elimination byproduct **8** was also isolated) in similar yields in a modified rearrangement condition of $TFA/Cl(CH_2)_2Cl$ at 60 °C (Scheme 5). The conversion rate for the *trans* isomer **2.4a** was faster than for the *cis* isomer **2.4b**, while the rate of the *trans*/*cis* mixture **2.4** fell between those of *trans*-**2.4a** and *cis*-**2.4b**. The rearranged product **3.4a** was determined as the (*S*,*S*)-configuration by LC−MS, ^1H NMR, ^{13}C NMR, and X-ray diffraction (Figure S-45, Supporting Information).

To understand these observations, we examined a molecular model of the isomers *trans*-**2.4a** and *cis*-**2.4b**. The aniline moiety of *trans*-**2.4a** can readily access to the 6-position of the pyrimidine nucleus for the Smiles rearrangement reaction, while the steric hindrance (neighboring substituent on the same side in the 7-membered ring) of the *cis* isomer **2.4b** prevented the aniline group from attacking the 6-position of the pyrimidine ring. Therefore, we propose that *cis*-**2.4b** must undergo conversion to the *trans* isomer **2.4a**[3c,d,9,11] before proceeding with the Smiles rearrangement to give **3.4a** under the current reaction conditions. It is further hypothesized that the conversion of compound **2.4b** to compound **2.4a** involved a carbocation intermediate as illustrated in Scheme 6.

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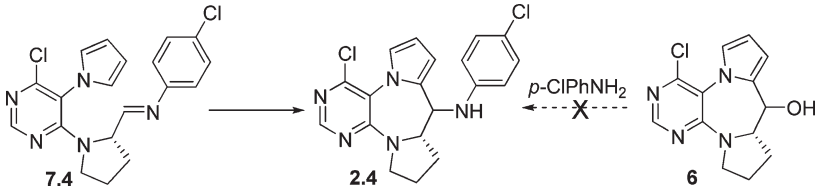
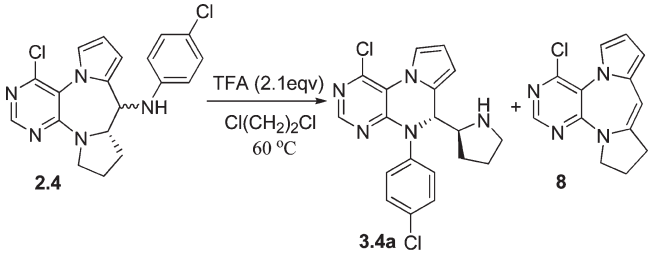
SCHEME 4. Possible Reactions Leading to Diazepines 2.4



SCHEME 5. Smiles Rearrangement of 2.4



2.4a (*trans*) $[\alpha]^{23}_D$ +83.6 (*c* 1.0, $CHCl_3$)	76% (7 h) $[\alpha]^{21}_D$ +423.2 (*c* 1.0, $CHCl_3$)	8%
2.4b (*cis*) $[\alpha]^{23}_D$ +348.8 (*c* 1.0, $CHCl_3$)	75% (13.5 h) $[\alpha]^{21}_D$ +411.8 (*c* 1.0, $CHCl_3$)	5%
2.4 (*trans*/*cis* = 1:2.1)	69% (10 h) $[\alpha]^{21}_D$ +405.6 (*c* 1.0, $CHCl_3$)	6%

Under the acidic conditions, loss of the aniline group in the *cis* isomer **2.4b** generates a carbocation **9**, which is reassociated with the aniline group via a S_N1 mechanism to give either the *trans* isomer **2.4a** or the *cis* isomer **2.4b**.[3c,d,9,11a] Subsequently, *trans* isomer **2.4a** proceeds to the Smiles rearrangement to give product **3.4a**, which drives the equilibrium to the direction of **2.4a**. The small amount of byproduct **8** was formed either from loss of a proton from intermediate **9** or direct aniline elimination of precursors **2.4a** and **2.4b**.[12]

To further validate our proposed carbocation process depicted in Scheme 6, a competition experiment was performed. Thus, the Smiles rearrangement reaction of the diastereomeric mixture (*trans*/*cis* = 1:2.1) **2.4** was carried out in the presence of 1 equiv of *p*-methoxyaniline, which produced a mixture of products **3.4a** and **3.1a** in a combined yield of 68% (**3.4a**:**3.1a** = 1.25:1) (Scheme 7). The formation of *p*-methoxyaniline-incorporated product **3.1a** provided the evidence that the Smiles rearrangement might indeed take place via carbocation intermediate **9** (the S_N2 replacement of *p*-chloroanilinyl by *p*-methoxyanilinyl had been excluded in the earlier experiment). The significant amount of anilinyl-exchanged product **3.1a** indicated that formation of carbocation **9** could be quite facile under the current rearrangement conditions.

In comparison to our previously reported Smiles rearrangement conditions of TFA−dichloromethane (DCM) at room temperature,[4a] the moderate elevation of reaction temperature required for diazepines **2.4** suggested that the presence of an additional ring in the substrate might increase the activation energy in the transition state. Consequently, the change of conditions could lead to the alteration reaction processes. For this reason, the reaction of diazepine **10** with 1 equiv of *p*-methoxyaniline was performed under the previous Smiles rearrangement conditions of TFA−DCM at room temperature. Surprisingly, the reaction produced the direct rearrangement product **11** in good yield (83%) and only a trace amount of the anilinyl-exchanged rearrangement product **12** (Scheme 8). This observation indicates that the Smiles rearrangement of diazepine **10** is more facile than the formation of the carbocation intermediate. The observed difference in reactivity between diazepines **10** and **2.4** could be attributed to the presence of the pyrrolidine moiety in diazepines **2.4**. It is likely that the steric hindrance and structural rigidity of the pyrrolidine ring slows down the Smiles rearrangement reaction and diverts the reaction more down the carbocation path in diazepine **2.4** (Scheme 6).

To further validate the reaction process, aldehyde **1** was reacted with several aromatic amines under the current tandem conditions (Scheme 9). In general, anilines with either electron-withdrawing (Cl) or electron-donating (MeO, Me) groups led to the desired pteridines **3a** in good yields (59−74%). The slightly higher yield for anilines with an electron-donating group (MeO, Me) compared to that for *p*-chloroaniline is consistent with formation of the imine intermediate as the key to this tandem iminium cyclization and Smiles rearrangement.

Conclusion

Mechanistic investigations of the previously communicated tandem iminium cyclization and Smiles rearrangement reactions[4] were carried out using a carefully designed chiral substrate **1** as a tool. Insights to the mechanism of this cascade reaction were obtained. First, the cascade reaction is a highly stereospecific process starting from the homochiral alcohol **5** and ending with a homochiral pteridine product **3a** in 59−74% overall yield for the three steps. Second, the formation of the kinetically favored *cis* cyclization product over the thermodynamically favored *trans* cyclization product could be rationalized by the formation of a Cram's chelate transition state (via intramolecular hydrogen bond). Third, the *cis*-diazepine **2.4b** must undergo equilibration to the *trans* isomer **2.4a** before proceeding to the Smiles rearrangement reaction, and the equilibration took place via a carbocation intermediate. Finally, the Smiles rearrangement of diazepine **10** without the additional pyrrolidine ring was much faster than the generation of a carbocation since very little exchange of the anilinyl moiety in the product was observed. These results reaffirmed the initially proposed cascade reaction involving an iminium cyclization followed by Smiles rearrangement in the unique molecular systems. The knowledge gained in these experiments could be useful in the design of new tandem reaction sequences for the synthesis of complex organic molecules from nature or with important biological activities. Further

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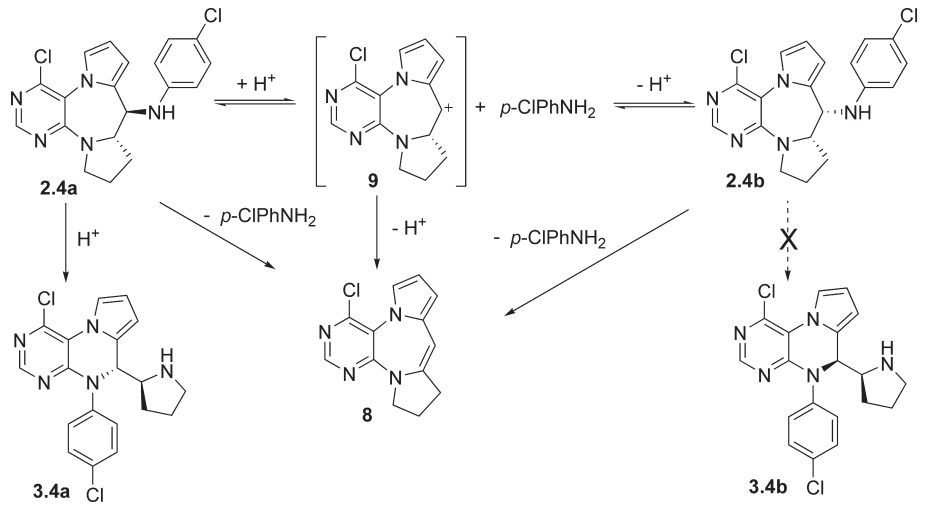
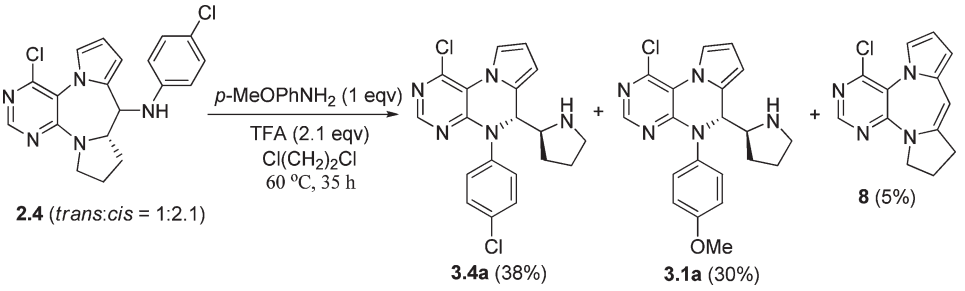
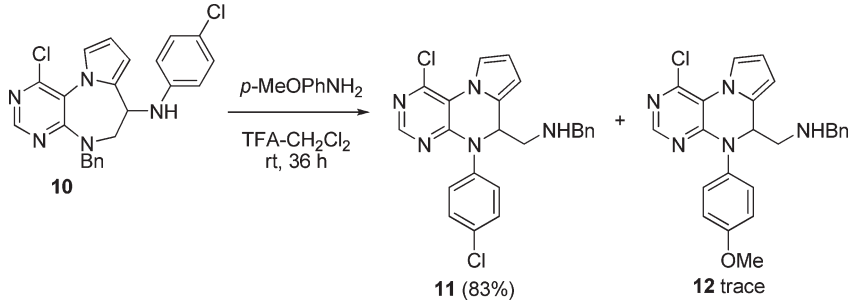
SCHEME 6. Proposed Rearrangement Processes



SCHEME 7. Competition Experiment 1



SCHEME 8. Competition Experiment 2



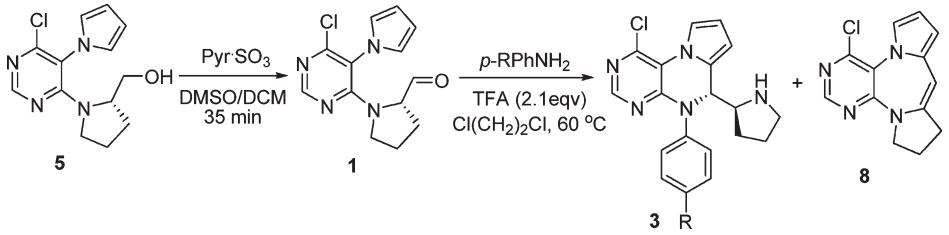
work is in progress to expand the strategy and methodology for the asymmetric synthesis of chiral heterocyclic molecules.

Experimental Section

General Consideration. Dichloromethane (DCM) was dried with P_2O_5 and distilled. All other commercial reagents were used as received without additional purification. The melting point was uncorrected. Mass spectra and HPLC data were recorded on a LC/MS system with ELSD. Optical rotations were determined with a digital polarimeter. The ^1H and ^{13}C NMR data were obtained on a 300 MHz NMR spectrometer with TMS as the internal standard and $CDCl_3$ as solvent unless otherwise stated. Multiplicities are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doubled doublet; br, broad. Coupling constants (*J* values) where noted are quoted in hertz.

(*S*)-(1-(6-Chloro-5-(1*H*-pyrrol-1-yl)pyrimidin-4-yl)pyrrolidin-2-yl)methanol (5). To a stirred solution of 4,6-dichloro-5-(1*H*-pyrrol-1-yl)pyrimidine (**4**) (5.0 g, 23.47 mmol) and L-prolinol (2.61 g, 25.82 mmol) in *n*-BuOH (80 mL) was added TEA (4.91 mL, 35.21 mmol). The resulting solution was stirred for 2 h at reflux. Then *n*-BuOH was evaporated, and the residue was diluted with DCM and washed with water. The organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash column chromatography (petroleum ether/EtOAc = 4:1 to 2:1, v/v) afforded 6.08 g (93%) of **5** as a white solid: mp 84−85 °C; $[\alpha]^{18}_D$ −56.0 (*c* 1.0, $CHCl_3$); ^1H NMR δ 8.30 (s, 1H), 6.70 (dd, 2H, J = 4.5, 2.7 Hz), 6.33 (dd, 2H, J = 4.5, 2.4 Hz), 4.44 (br, 1H), 3.93 (br, 1H), 3.68 (d, 2H, J = 5.7 Hz), 2.93 (t, 2H, J = 6.3 Hz), 1.97−1.69 (m, 4H); ^{13}C NMR δ

SCHEME 9. Tandem Reaction of Aldehyde 1 with Anilines



3.1a R = MeO (74%, 11 h) (5%)
$[\alpha]^{21}_D$ +382.2 (*c* 1.0, $CHCl_3$)

3.2a R = Me (71%, 14 h), (6%)
$[\alpha]^{21}_D$ +376.8 (*c* 1.0, $CHCl_3$)

3.3a R = H (66%, 16 h) (5%)
$[\alpha]^{21}_D$ +444.0 (*c* 1.0, $CHCl_3$)

3.4a R = Cl (59%, 18 h) (6%)
$[\alpha]^{21}_D$ +416.2 (*c* 1.0, $CHCl_3$)

160.0, 158.2, 155.7, 124.9, 124.3, 116.5, 110.0, 109.9, 65.1, 62.6, 45.9, 27.6, 24.5; MS (ESI) *m*/*z* 279.1 [M + H^+]. Anal. Calcd for $C_{13}H_{15}ClN_4O$: C, 56.02; H, 5.42; N, 20.10. Found: C, 55.89; H, 5.40; N, 20.10.

General Procedure for the Synthesis of Pyrimido[4,5-*b*]dipyrrolo[1,2-*d*:1′,2′-*g*][1,4]diazepin-9-amine (2). (*S*)-(1-(6-Chloro-5-(1*H*-pyrrol-1-yl)pyrimidin-4-yl)pyrrolidin-2-yl)methanol (**5**) (139 mg, 0.50 mmol) in 6 mL of DMSO−DCM (1:1) was treated with TEA (0.703 mL, 5.0 mmol). A solution of SO_3−pyridine (481 mg, 3.0 mmol) in 4 mL of DMSO−DCM (3:1) was added, and the mixture was stirred for 35 min at ambient temperature. The reaction solution was then diluted with DCM (20 mL), washed twice with 10% citric acid and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give crude aldehyde **1**. The crude **1** was dissolved in $Cl(CH_2)_2Cl$ (18 mL). To the resulting solution was added the appropriate amine (0.6 mmol) followed by TFA (78 μL, 1.05 mmol). The mixture was stirred for 10 min at room temperature, washed with saturated aqueous Na_2CO_3, dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (petroleum ether/EtOAc = 4:1 to 2:1, v/v) afforded the desired product **2**.

(9a*S*)-4-Chloro-*N*-(4-methoxyphenyl)-9a,10,11,12-tetrahydro-9*H*-pyrimido[4,5-*b*]dipyrrolo[1,2-*d*:1′,2′-*g*][1,4]diazepin-9-amine (2.1). Yield: 83%. ^{1}H NMR (**2.1a**/**2.1b**, 8.29 ppm/8.27 ppm) indicated the ratio of the two isomers of **2.1** to be 1:9.1 (**2.1a**/**2.1b**): ^{1}H NMR δ 8.29 (s, 0.11H), 8.27 (s, 1.00H), 6.99 (dd, 0.10H, *J* = 4.5, 1.5 Hz), 6.93 (dd, 1.35H, *J* = 2.7, 1.5 Hz), 6.79−6.58 (m, 8.90H), 6.21−6.13 (m, 3.21H), 6.06−6.04 (m, 0.08H), 4.67 (s, 1.67H), 4.46 (d, 0.05H, *J* = 7.8 Hz), 4.09−4.04 (m, 1.70H), 3.90−3.84 (m, 3.50H), 3.75 (s, 1.23H), 3.73 (s, 0.39H), 3.71 (s, 4.66H), 2.36−2.28 (m, 0.13H), 2.18−2.04 (m, 5.79H), 1.95−1.79 (m, 2.40H); MS (ESI) *m*/*z* 382.1 [M + H^+]. Anal. Calcd for $C_{20}H_{20}ClN_5O$: C, 62.91; H, 5.28; N, 18.34. Found: C, 63.17; H, 5.30; N, 18.29.

(9a*S*)-4-Chloro-*N*-(4-methylphenyl)-9a,10,11,12-tetrahydro-9*H*-pyrimido[4,5-*b*]dipyrrolo[1,2-*d*:1′,2′-*g*][1,4]diazepin-9-amine (2.2). Yield: 85%. ^{1}H NMR (**2.2a**/**2.2b**, 8.29 ppm/8.27 ppm) indicated the ratio of the two isomers of **2.2** to be 1:3.7 (**2.2a**/**2.2b**): ^{1}H NMR δ 8.29 (s, 0.27H), 8.27 (s, 1.00H), 7.00−6.93 (m, 5.34H), 6.62−6.54 (m, 3.81H), 6.20−6.15 (m, 3.17H), 6.05−6.04 (m, 0.23H), 4.73 (s, 1.53H), 4.53 (d, 0.26H, *J* = 8.7), 4.07 (dd, 1.63H, *J* = 10.2, 5.7), 3.91−3.68 (m, 4.38H), 2.35−2.25 (m, 0.74H), 2.23 (s, 1.13H), 2.20 (s, 4.52H), 2.18−1.99 (m, 5.42H), 1.89−1.79 (m, 2.19H); MS (ESI) *m*/*z* 366.1 [M + H^+]. Anal.Calcd for $C_{20}H_{20}ClN_5$: C, 65.66; H, 5.51; N, 19.14. Found: C, 65.55; H, 5.49; N, 19.08.

(9a*S*)-4-Chloro-*N*-phenyl-9a,10,11,12-tetrahydro-9*H*-pyrimido-[4,5-*b*]dipyrrolo[1,2-*d*:1′,2′-*g*][1,4]diazepin-9-amine (2.3). Yield: 80%. ^{1}H NMR (**2.3a**/**2.3b**, 8.30 ppm/8.28 ppm) indicated the ratio of two isomers of **2.3** to be 1:3.2 (**2.3a**/**2.3b**): ^{1}H NMR δ 8.30 (s, 0.31H), 8.28 (s, 1.00H), 7.21−7.11 (m, 3.66H), 7.01−6.99 (m, 0.37H), 6.94 (t, 1.21H, *J* = 2.4), 6.78−6.64 (m, 5.75H), 6.19 (t, 0.54H, *J* = 1.5), 4.78 (s, 1.47H), 4.58 (d, 0.44H, *J* = 8.4), 4.09 (dd, 1.55H, *J* = 10.5, 5.4), 4.00−3.70 (m, 4.77H), 2.37−2.28 (m, 0.81H), 2.22−2.00 (m, 6.42H), 1.95−1.72 (m, 4.66H); MS (ESI) *m*/*z* 352.1 [M + H^+]. Anal. Calcd for $C_{19}H_{18}ClN_5$: C, 64.86; H, 5.16; N, 19.91. Found: C, 64.78; H, 5.15; N, 19.83.

(9a*S*)-4-Chloro-*N*-(4-chlorophenyl)-9a,10,11,12-tetrahydro-9*H*-pyrimido[4,5-*b*]dipyrrolo[1,2-*d*:1′,2′-*g*][1,4]diazepin-9-amine (2.4). Yield: 86%. ^{1}H NMR (**2.4a**/**2.4b**, 8.30 ppm/8.27 ppm) indicated the ratio of two isomers of **2.4** to be 1:2.1 (**2.4a**/**2.4b**): ^{1}H NMR δ 8.30 (s, 0.48H), 8.27 (s, 1.00H), 7.14−7.05 (m, 3.77H), 7.03−6.99 (m, 0.60H), 6.93 (t, 1.14H, *J* = 2.4 Hz), 6.66−6.51 (m, 4.22H), 6.23−6.16 (m, 3.24H), 6.01 (t, 0.62H, *J* = 1.8 Hz), 4.72 (d, 1.34H, *J* = 5.7 Hz), 4.52 (t, 0.62H, *J* = 9.0 Hz), 4.18−4.02 (m, 1.60H), 4.01−3.67 (m, 5.61H), 3.48 (d, 1.13H, *J* = 6.0 hz), 2.38−1.71 (m, 8.94H); MS (ESI) *m*/*z* 385.9 [M + H^+]. Anal. Calcd for $C_{19}H_{17}Cl_2N_5$: C, 59.08; H, 4.44; N, 18.13. Found: C, 58.94; H, 4.43; N, 18.05. A pure sample of major product **2.4b** was obtained by recrystallization from *i*-PrOH while the one of the minor product **2.4a** was purified by flash chromatography (petroleum ether/EtOAc = 20:1 to 15:1, v/v). **(9*S*,9a*S*)-4-Chloro-*N*-(4-chlorophenyl)-9a,10,11,12-tetrahydro-9*H*-pyrimido[4,5-*b*]dipyrrolo[1,2-*d*:1′,2′-*g*]-[1,4]diazepin-9-amine (2.4a):** mp 79−82 °C; $[\alpha]^{23}_D$ +83.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 8.30 (s, 1H), 7.14−7.10 (m, 2H), 7.01 (dd, 1H, *J* = 2.7, 1.8 Hz), 6.64−6.59 (m, 2H), 6.20 (t, 1H, *J* = 3.3 Hz), 6.02 (d, 1H, *J* = 3.3 Hz), 4.52 (t, 1H, *J* = 9.0 Hz), 4.00−3.70 (m, 4H), 2.32−2.28 (m, 1H), 2.05−2.01 (m, 1H), 1.85−1.72 (m, 2H); ^{13}C NMR δ 154.2, 153.9, 152.6, 145.3, 135.0, 129.2, 124.5, 123.1, 115.3, 114.9, 109.0, 105.5, 69.8, 53.9, 51.4, 32.5, 22.0; MS (ESI) *m*/*z* 386.1 [M + H^+]. Anal.Calcd for $C_{19}H_{17}Cl_2N_5$: C, 59.08; H, 4.44; N, 18.13. Found: C, 58.87; H, 4.46; N, 18.09. **(9*R*,9a*S*)-4-Chloro-*N*-(4-chlorophenyl)-9a,10,11,12-tetrahydro-9*H*-pyrimido[4,5-*b*]-dipyrrolo[1,2-*d*:1′,2′-*g*][1,4]diazepin-9-amine (2.4b):** mp 171−172 °C; $[\alpha]^{23}_D$ +348.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 8.27 (s, 1H), 7.07 (d, 2H, *J* = 8.7), 6.93 (s, 1H), 6.57 (d, 2H, *J* = 8.7), 6.19 (d, 2H, *J* = 1.8), 4.72 (d, 1H, *J* = 7.2), 4.11−4.06 (m, 1H), 3.90−3.85 (m, 2H), 3.47 (d, 1H, *J* = 6.9), 2.20−1.83 (m, 4H); ^{13}C NMR δ 154.1, 153.4, 152.0, 145.2, 133.0, 128.9, 125.0, 123.3, 115.7, 115.3, 109.0, 108.7, 66.7, 52.2, 51.4, 31.5, 22.2; MS (ESI) *m*/*z* 386.0 [M + H^+]. Anal. Calcd for $C_{19}H_{17}Cl_2N_5$: C, 59.08; H, 4.44; N, 18.13. Found: C, 58.98; H, 4.43; N, 18.08. Further recrystallization of compound **2.4b** by slow evaporation from DCM/MeOH afforded a colorless crystal for X-ray diffraction analysis (see the CIF in the Supporting Information).

(9a*S*)-4-Chloro-*N*-(4-nitrophenyl)-9a,10,11,12-tetrahydro-9*H*-pyrimido[4,5-*b*]dipyrrolo[1,2-*d*:1′,2′-*g*][1,4]diazepin-9-amine (2.5). Yield: 69%. ^{1}H NMR (**2.5a**/**2.5b**, 8.31 ppm/8.28 ppm) indicated the ratio of two isomers of **2.5** to be 1:1.0 (**2.5a**/**2.5b**): ^{1}H NMR δ 8.31 (s, 1.00H), 8.28 (s, 1.00H), 8.10 (d, 2.77H, J = 9.0 Hz), 8.04 (d, 2.68H, J = 9.0 Hz), 7.05−7.04 (m, 1.18H), 6.98−6.96 (m, 1.21H), 6.70−6.64 (m, 6.32H), 6.31−6.29 (m, 1.47H), 6.24−6.20 (m, 2.77H), 6.02−6.01 (m, 1.63H), 4.88 (d, 1.29H, J = 6.3 Hz), 4.71−4.69 (m, 3.12H), 4.30 (d, 1.37H, J = 7.2 Hz), 4.16−4.11 (m, 1.74H), 4.02−3.89 (m, 6.72H), 3.77 (dd, 2.28H, J = 12.3, 7.6 Hz), 2.34−2.22 (m, 4.00H), 2.12−1.80 (m, 13.63H); MS (ESI) m/z 397.1 [M + H$^+$]. Anal. Calcd for $C_{19}H_{17}ClN_6O_2$: C, 57.51; H, 4.32; N, 21.18. Found: C, 57.44; H, 4.31; N, 21.12.

(9a*S*)-4-Chloro-9a,10,11,12-tetrahydro-9*H*-pyrimido[4,5-*b*]dipyrrolo[1,2-*d*:1′,2′-*g*][1,4]diazepin-9-ol (6). (*S*)-(1-(6-Chloro-5-(1*H*-pyrrol-1-yl)pyrimidin-4-yl)pyrrolidin-2-yl)methanol (**5**) (139 mg, 0.50 mmol) in 6 mL of DMSO−DCM (1:1) was treated with TEA (0.703 mL, 5.0 mmol). A solution of SO_3−pyridine (481 mg, 3.0 mmol) in 4 mL of DMSO−DCM (3:1) was added, and the mixture was stirred for 35 min at ambient temperature. The reaction solution was then diluted with DCM (20 mL), washed twice with 10% citric acid and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give crude aldehyde **1**. The crude **1** was dissolved in $Cl(CH_2)_2Cl$ (18 mL). To the above solution was added TFA (78 μL, 1.05 mmol). The mixture was stirred for 20 min at ambient temperature, washed with saturated aqueous Na_2CO_3, dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (petroleum ether/EtOAc = 4:1 to 2:1, v/v) afforded 4 mg (3%) of compound **6a** and 114 mg (83%) of compound **6b**.

(9*S*,9a*S*)-4-Chloro-9a,10,11,12-tetrahydro-9*H*-pyrimido[4,5-*b*]dipyrrolo[1,2-*d*:1′,2′-*g*][1,4]diazepin-9-ol (6a): mp 172−174 °C; ^{1}H NMR δ 8.25 (s, 1H), 7.04−7.02 (m, 1H), 6.27 (t, 1H, J = 3.0 Hz), 6.24−6.22 (m, 1H), 4.71 (d, 1H, J = 8.4 Hz), 3.96−3.86 (m, 1H), 3.75−3.62 (m, 2H), 2.38−2.34 (m, 1H), 2.12−2.03 (m, 1H), 1.90−1.73 (m, 3H); MS (ESI) m/z 277.1 [M + H$^+$].

(9*R*,9a*S*)-4-Chloro-9a,10,11,12-tetrahydro-9*H*-pyrimido[4,5-*b*]dipyrrolo[1,2-*d*:1′,2′-*g*][1,4]diazepin-9-ol (6b): mp 238−239 °C; $[\alpha]^{23}_D$ +459.0 (c 1.0, $CHCl_3$); ^{1}H NMR δ 8.20 (s, 1H), 7.03 (dd, 1H, J = 3.0, 1.8), 6.18 (t, 1H, J = 3.3), 6.14 (dd, 1H, J = 3.6, 1.5), 4.96 (s, 1H), 3.89−3.74 (m, 3H), 2.16−2.00 (m, 4H), 1.86−1.76 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 155.0, 152.9, 150.1, 135.5, 124.8, 116.2, 108.4, 107.0, 67.8, 64.2, 51.4, 30.8, 21.9; MS (ESI) m/z 277.0 [M + H$^+$]. Anal. Calcd for $C_{13}H_{13}ClN_4O$: C, 56.42; H, 4.74; N, 20.25. Found: C, 56.17; H, 4.72; N, 20.27.

General Procedure for the Synthesis of Pyrrolo[1,2-*f*]pteridine 3.4a via Smiles Rearrangement. To a stirred solution of **2.4a**, **2.4b**, or **2.4** (**2.4a**/**2.4b** = 1:2.1) (193 mg, 0.5 mmol) in $Cl(CH_2)_2Cl$ (18 mL) was added TFA (78 μL, 1.05 mmol). After the mixture was stirred for the corresponding time at 60 °C, the solvent was removed in vacuo and DCM (30 mL) was added. The organic layers were washed with saturated aqueous $NaHCO_3$ (15 mL), dried over $MgSO_4$, concentrated in vacuo, and purified by flash chromatography (MeOH/DCM = 100:1 to 20:1, v/v) to afford the desired products **3.4a** and **8**.

(*S*)-1-Chloro-5-(4-chlorophenyl)-6-((*S*)-pyrrolidin-2-yl)-5,6-dihydropyrrolo[1,2-*f*]pteridine 3.4a. Compound **2.4a** as starting material: **3.4a**, 76%; mp 111−113 °C; $[\alpha]^{21}_D$ +423.2 (c 1.0, $CHCl_3$); ^{1}H NMR δ 8.09 (s, 1H), 7.96 (d, 1H, J = 1.5 Hz), 7.42 (d, 2H, J = 8.4 Hz), 7.36 (d, 2H, J = 8.1 Hz), 6.43 (t, 1H, J = 2.7 Hz), 6.13 (t, 1H, J = 1.5 Hz), 4.79 (d, 1H, J = 4.2 Hz), 3.58−3.52 (m, 1H), 2.74−2.67 (m, 1H), 2.38−2.31 (m, 1H), 1.83−1.74 (m, 1H), 1.56−1.35 (m, 4H); ^{13}C NMR δ 154.1, 151.5, 142.4, 140.6, 132.8, 129.5, 128.8, 125.3, 119.9, 118.1, 111.5 107.2, 63.4, 61.3, 46.6, 29.0, 25.9; MS (ESI) m/z 386.1 [M + H$^+$]. Compound **2.4b** as starting material: **3.4a**, 75%; mp 110−112 °C; $[\alpha]^{21}_D$ +411.8 (c 1.0, $CHCl_3$); ^{1}H NMR δ 8.09 (s, 1H), 7.97 (d, 1H, J = 1.8 Hz), 7.42 (d, 2H, J = 8.7 Hz), 7.36 (d, 2H, J = 8.7 Hz), 6.43 (t, 1H, J = 3.3 Hz), 6.14−6.13 (m, 1H), 4.79 (d, 1H, J = 4.2 Hz), 3.58−3.52 (m, 1H), 2.74−2.69 (m, 1H), 2.38−2.33 (m, 1H), 1.84−1.74 (m, 1H), 1.54−1.41 (m, 4H); ^{13}C NMR δ 154.2, 151.6, 142.4, 140.6, 132.8, 129.6, 128.9, 125.4, 120.0, 118.2, 111.5, 107.1, 63.5, 61.4, 46.7, 29.0, 25.9; MS (ESI) m/z 386.0 [M + H$^+$]. Compound **2.4** (**2.4a**/**2.4b** = 1:2.1) as starting material: **3.4a**, 69%; mp 110−112 °C; $[\alpha]^{21}_D$ +405.6 (c 1.0, $CHCl_3$); ^{1}H NMR δ 8.09 (s, 1H), 7.97 (dd, H, J = 3.0, 1.5 Hz), 7.42 (d, 2H, J = 8.7 Hz), 7.36 (d, 2H, J = 9.0 Hz), 6.43 (t, 1H, J=3.3 Hz), 6.13 (dd, 1H, J = 3.3, 1.2 Hz), 4.79 (d, 1H, J = 4.2 Hz), 3.58−3.52 (m, 1H), 2.74−2.67 (m, 1H), 2.38−2.31 (m, 1H), 1.83−1.74 (m, 1H), 1.57−1.37 (m, 4H); ^{13}C NMR δ 154.2, 151.6, 142.4, 140.6, 132.8, 129.6, 128.9, 125.3, 120.0, 118.2, 111.5, 107.2, 63.4, 61.4, 46.6, 29.0, 25.9; MS (ESI) m/z 386.0 [M + H$^+$]. Recrystallization of compound **3.4a** by slow evaporation from DCM/hexane/Et_2O afforded a colorless crystal for X-ray diffraction analysis (see the CIF in the Supporting Information).

(*Z*)-4-Chloro-11,12-dihydro-10*H*-pyrimido[4,5-*b*]dipyrrolo[1,2-*d*:1′,2′-*g*][1,4]diazepine (8): 5−8% yield; oil; ^{1}H NMR δ 8.12 (s, 1H), 6.75 (d, 1H, J = 3.0 Hz), 6.24 (t, 1H, J = 3.3 Hz), 5.91−5.90 (m, 1H), 5.59 (s, 1H), 3.75 (t, 2H, J = 6.9 Hz), 2.50 (t, 2H, J = 7.5 Hz), 1.98−1.89 (m, 2H); MS (ESI) m/z 259.1 [M + H$^+$].

Competition Experiment 1. To a stirred solution of **2.4** (**2.4a**/**2.4b** = 1:2.1) (97 mg, 0.25 mmol) in $Cl(CH_2)_2Cl$ (9 mL) were added *p*-methoxyaniline (31 mg, 0.25 mmol) and TFA (40 μL, 0.525 mmol). After the mixture was stirred for 35 h at 60 °C, the solvent was removed in vacuo, and DCM (40 mL) was added. The organic layers were washed with saturated aqueous $NaHCO_3$ (20 mL), dried over $MgSO_4$, and concentrated in vacuo to afford a crude mixture of **3.4a** and **3.1a** (^{1}H NMR of 8.09 ppm/8.06 ppm indicated the ratio of **3.4a** and **3.1a** to be 1.25:1). The residue was purified by flash column chromatography (petroleum ether/EtOAc = 2:1, v/v) to afford 66 mg (68%) of a mixture of **3.4a** and **3.1a** (ratio 1.25:1) and 3 mg (5%) of **8**.

Synthesis of 5-Benzyl-1-chloro-*N*-(4-chlorophenyl)-6,7-dihydro-5*H*-pyrimido[4,5-*b*]pyrrolo[1,2-*d*][1,4]diazepin-7-amine (10). 6-[*N*-Benzyl(2-ethanol)amino]-4-chloro-5-pyrrol-1-yl-pyrimidine[4a] (984 mg, 3.0 mmol) in 20 mL of DMSO−DCM (1:1) was treated with TEA (4.2 mL, 30 mmol). A solution of SO_3−pyridine (2.8 g, 18.0 mmol) in 20 mL of DMSO−DCM (1:1) was added, and the mixture was stirred for 35 min at ambient temperature. The reaction solution was then diluted with DCM (60 mL), washed twice with 10% citric acid and brine, dried over $MgSO_4$, and filtered to give crude aldehyde[1a] in DCM. To the above solution was added *p*-chloroaniline (383 mg, 3.0 mmol). The mixture was stirred for 1 h at ambient temperature, washed with saturated aqueous Na_2CO_3, dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (petroleum ether/EtOAc = 4:1 to 2:1, v/v) afforded 770 mg (59%) of product **10**: mp 203−204 °C; ^{1}H NMR δ 8.35 (s, 1H), 7.31−7.23 (m, 5H), 7.01−6.97 (m, 3H), 6.37 (d, 2H, J = 8.7 Hz), 6.25 (t, 1H, J = 3.3 Hz), 6.12 (dd, 1H, J = 3.3, 1.2 Hz), 4.94 (br, 1H), 4.87 (br, 1H), 4.69−4.63 (m, 1H), 3.77−3.73 (m, 2H), 3.65−3.58 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 156.8, 153.4, 152.5, 145.8, 136.8, 134.2, 128.42, 128.39, 127.4, 127.1, 123.5, 120.1, 116.5, 114.6, 108.5, 104.8, 58.8, 54.1, 47.1; MS (ESI): m/z 436.1 [M + H$^+$]. Anal. Calcd for $C_{23}H_{19}Cl_2N_5$: C, 63.31; H, 4.39; N, 16.05. Found: C, 63.22; H, 4.38; N, 15.99.

Competition Experiment 2. To a stirred solution of 5-benzyl-1-chloro-*N*-(4-chlorophenyl)-6,7-dihydro-5*H*-pyrimido[4,5-*b*]-pyrrolo[1,2-*d*][1,4]diazepin-7-amine (**10**) (43.6 mg, 0.1 mmol) in DCM (3 mL) were added *p*-methoxyaniline (12.3 mg, 0.1 mmol) and TFA (13 μL, 0.18 mmol). The mixture was stirred for 36 h at room temperature (a trace amount with molecular ion corresponding to 1-chloro-5,6-dihydro-6-[(benzylamino)methyl]-5-(4-methoxyphenyl)pyrrolo[1,2-*f*]pteridine (**12**) was detected by LC−MS) and then washed with saturated aqueous $NaHCO_3$ (1.5 mL), dried over $MgSO_4$, and concentrated in vacuo.

Purification by flash chromatography (petroleum ether/EtOAc = 4:1 to 2:1, v/v) afforded 36 mg (83%) of 1-chloro-5,6-dihydro-6-[(benzylamino)methyl]-5-(4-chlorophenyl)pyrrolo[1,2-*f*]-pteridine (**11**): mp 138−140 °C; ^{1}H NMR δ 8.12 (s, 1H), 7.98 (dd, 1H, J = 3.3, 1.2), 7.38−7.33 (m, 2H), 7.33−7.22 (m, 3H), 7.21−7.15 (m, 2H), 7.10 (dd, 2H, J = 7.5, 1.8), 6.44 (t, 1H, J = 3.3), 6.15 (dd, 1H, J = 3.6, 1.5), 5.02 (dd, 1H, J = 6.3, 3.9), 3.69 (A of AB, 1H, J = 13.2), 3.60 (B of AB, 1H, J = 13.2), 2.96 (dd, 1H, J = 12.3, 3.9), 2.86 (dd, 1H, J = 12.3, 6.3); MS (ESI) m/z 436.1 [M + H$^+$].

General Procedure for the Synthesis of 5,6-Dihydropyrrolo-[1,2-*f*]pteridine 3a via Tandem Iminium Cyclization and Smiles Rearrangement. (*S*)-(1-(6-Chloro-5-(1*H*-pyrrol-1-yl)pyrimidin-4-yl)pyrrolidin-2-yl)methanol (**5**) (139 mg, 0.50 mmol) in 6 mL of DMSO−DCM (1:1) was treated with TEA (0.703 mL, 5.0 mmol). A solution of SO_3−pyridine (481 mg, 3.0 mmol) in 4 mL of DMSO−DCM (3:1) was added, and the mixture was stirred for 35 min at ambient temperature. The reaction solution was then diluted with DCM (20 mL), washed twice with 10% citric acid and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give crude aldehyde **1**. The crude **1** was dissolved in $Cl(CH_2)_2Cl$ (18 mL). To the resulting solution was added the appropriate amine (0.6 mmol) followed by TFA (78 μL, 1.05 mmol). After the mixture was stirred for the corresponding time at 60 °C, the solvent was removed in vacuo and DCM (30 mL) was added. The organic layers were washed with saturated aqueous $NaHCO_3$ (15 mL), dried over $MgSO_4$, concentrated in vacuo, and purified by flash chromatography (MeOH/DCM = 100:1 to 20:1, v/v) to afford the desired products **3a** and **8**.

(***S***)**-1-Chloro-5-(4-methoxyphenyl)-6-((*S*)-pyrrolidin-2-yl)-5,6-dihydropyrrolo[1,2-*f*]pteridine (3.1a):** 74%; mp: 60−62 °C; $[\alpha]^{21}_D$ +382.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 8.06 (s, 1H), 7.97 (d, 1H, J = 2.1 Hz), 7.31 (d, 2H, J = 8.7 Hz), 6.97 (d, 2H, J = 9.0 Hz), 6.43 (t, 1H, J = 3.0 Hz), 6.11 (d, 1H, J = 2.4 Hz), 4.75 (d, 1H, J = 3.6 Hz), 3.84 (s, 3H), 3.58−3.54 (m, 1H), 2.74−2.67 (m, 1H), 2.40−2.34 (m, 1H), 1.78−1.72 (m, 1H), 1.52−1.40 (m, 4H); ^{13}C NMR δ 158.6, 154.6, 151.7, 141.8, 134.5, 129.2, 125.4, 119.9, 117.5, 114.6, 111.4, 106.9, 63.7, 61.1, 55.5, 46.6, 28.9, 25.9; MS (ESI) m/z 382.3 [M + H$^+$]; Anal. Calcd for $C_{20}H_{20}ClN_5O$: C, 62.91; H, 5.28; N, 18.34. Found: C, 62.67; H, 5.30; N, 18.31.

(***S***)**-1-Chloro-5-(4-methylphenyl)-6-((*S*)-pyrrolidin-2-yl)-5,6-dihydropyrrolo[1,2-*f*]pteridine (3.2a):** 71% yield; mp 68−70 °C; $[\alpha]^{21}_D$ +376.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 8.07 (s, 1H), 7.97 (d, 1H, J = 1.5 Hz), 7.34−7.10 (m, 4H), 6.43 (t, 1H, J = 3.0 Hz), 6.11 (d, 1H, J = 2.4 Hz), 4.78 (d, 1H, J = 3.9 Hz), 3.59−3.55 (m, 1H), 2.74−2.66 (m, 1H), 2.39−2.31 (m, 4H), 1.78−1.72 (m, 1H), 1.54−1.40 (m, 4H); ^{13}C NMR δ 154.5, 151.7, 141.9, 139.3, 137.4, 130.0, 127.6, 125.4, 119.8, 117.7, 111.4, 106.9, 63.5, 61.2, 46.6, 28.9, 25.9, 21.2; MS (ESI): m/z 365.9 [M + H$^+$]; Anal. Calcd for $C_{20}H_{20}ClN_5$: C, 65.66; H, 5.51; N, 19.14. Found: C, 65.44; H, 5.53; N, 19.13.

(***S***)**-1-Chloro-5-phenyl-6-((*S*)-pyrrolidin-2-yl)-5,6-dihydropyrrolo[1,2-*f*]pteridine (3.3a):** 66% yield; mp 118−120 °C; $[\alpha]^{21}_D$ +444.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 8.09 (s, 1H), 7.97 (d, 1H, J = 1.8 Hz), 7.48−7.30 (m, 5H), 6.43 (t, 1H, J = 3.3 Hz), 6.12 (d, 1H, J = 2.4 Hz), 4.82 (d, 1H, J = 3.9 Hz), 3.62−3.56 (m, 1H), 2.75−2.67 (m, 1H), 2.39−2.32 (m, 1H), 1.81−1.73 (m, 1H), 1.52−1.40 (m, 4H); ^{13}C NMR δ 154.3, 151.6, 142.1, 129.3, 127.5,127.3, 125.5, 119.8, 117.9,111.4, 106.9, 63.4, 61.3, 46.6, 28.9, 25.8; MS (ESI) m/z 351.9 [M + H$^+$]. Anal. Calcd for $C_{19}H_{18}ClN_5$: C, 64.86; H, 5.16; N, 19.91. Found: C, 64.66; H, 5.14; N, 19.86.

(***S***)**-1-Chloro-5-(4-chlorophenyl)-6-((*S*)-pyrrolidin-2-yl)-5,6-dihydropyrrolo[1,2-*f*]pteridine (3.4a):** 59% yield; mp 110−112 °C; $[\alpha]^{21}_D$ +416.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 8.09 (s, 1H), 7.97 (d, 1H, J = 1.5 Hz), 7.42 (d, 2H, J = 8.4 Hz), 7.36 (d, 2H, J = 8.7 Hz), 6.43 (t, 1H, J = 3.3 Hz), 6.13 (d, 1H, J = 2.1 Hz), 4.78 (d, 1H, J = 3.9 Hz), 3.57−3.52 (m, 1H), 2.72−2.67 (m, 1H), 2.37−2.32 (m, 1H), 1.80−1.74 (m, 1H), 1.52−1.40 (m, 4H); ^{13}C NMR δ 154.2, 151.6, 142.4, 140.6, 132.8, 129. 6, 128.9, 125.4, 120.0, 118.2, 111.5, 107.1, 63.5, 61.3, 46.6, 29.0, 25.9; MS (ESI) m/z 386.0 [M + H$^+$]. Anal. Calcd for $C_{19}H_{17}Cl_2N_5$: C, 59.08; H, 4.44; N, 18.13. Found: C, 58.87; H, 4.42; N, 18.05.

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Supporting Information Available: Copies of LC−MS and NMR spectra for all products and crystallographic data of **2.4b** and **3.4a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.