

**Samarium Diiodide-Induced Radical Cyclization of Oxime Ether
Connected with Formyl Group:
Synthesis of 4-Pyrimidinyl- and 4-Purinylypyrrolidin-3-ol
Nucleoside Analogues**

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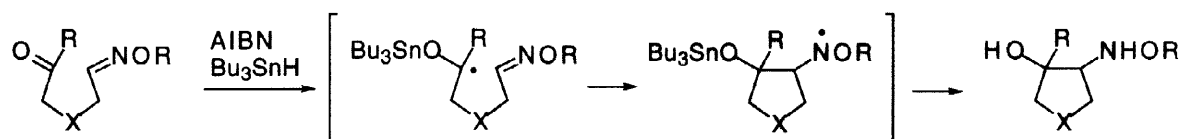
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Abstract: SmI₂-induced 5-*exo-trig* radical cyclization of oxime ether intramolecularly connected with the formyl group was found to be particularly effective for preparing cyclic *trans*-amino alcohol in good chemical yield with a high degree of stereoselectivity. Its successful application to the synthesis of a novel class of 4-pyrimidinyl- and 4-purinylypyrrolidin-3-ol nucleoside analogues is also described.
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INTRODUCTION

Strategies involving radical reactions have become preeminent tools in organic synthesis.¹ Free radical-mediated cyclization has particularly developed as a powerful method for preparing various type of cyclic compounds *via* carbon-carbon bond-forming processes. Although a number of extensive investigations into radical reaction were reported in recent years, the majority of these employ methods utilizing conventional radical acceptors such as alkenes or typical radical precursors such as halides, selenides and xanthates.² It is important to note that one drawback in the traditional procedures using such radical acceptors and precursors is loss of the inherent functional groups. Our laboratory is interested in developing effective and convenient methods for the synthesis of highly functionalized cyclic compounds. For this purpose, we have focused our efforts on the radical reactions using aldehydes and ketones as a radical precursor and/or oxime ether group as a radical acceptor.^{3,4} We recently reported the first example of the tributyltin hydride-induced radical cyclization of oxime ethers which were intramolecularly connected with aldehyde or ketone.⁵ This radical cyclization would be initiated by the addition of stannyl radical, generated from Bu₃SnH and AIBN, to the oxygen atom of the carbonyl group to form the *O*-stannyl ketyl radical which would be then intramolecularly trapped by the oxime ether group. Our newly-developed reaction is a facile and practical method to prepare the highly

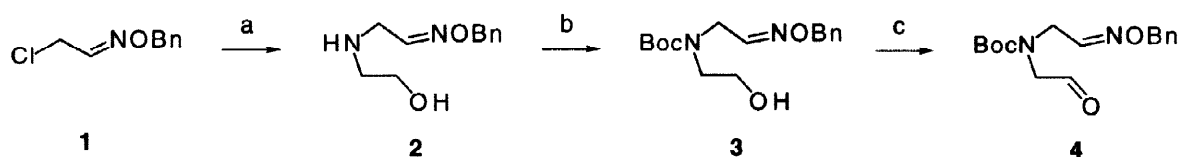


functionalized 5-, 6- and 7-membered compounds that retain the hydroxyl and amino functional groups, although a mixture of two diastereoisomeric products was obtained with low stereoselectivity. In this paper, we describe in detail the stereoselective radical cyclization of oxime ether intramolecularly connected with the formyl group based on the chemistry of samarium (II) diiodide (SmI_2), and also its successful application to the synthesis of a novel class of 4-pyrimidinyl- and 4-purinylypyrrolidin-3-ol nucleoside analogues.

RESULTS AND DISCUSSION

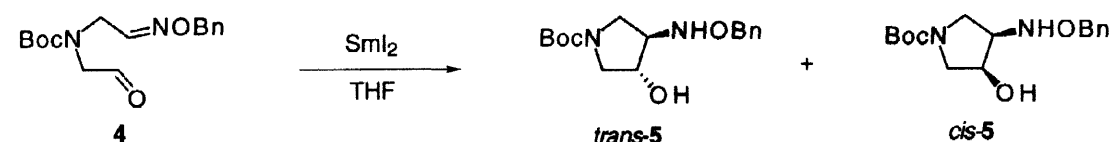
SmI₂-induced cyclization of oxime ether connected with formyl group

Preparation of oxime ether **4**, which is a requisite substrate for the following radical cyclization, is shown in Scheme 1. Treatment of α -chloroacetaldoxime ether **1**⁶ with commercially available 2-aminoethanol gave the secondary amine **2** in 88% yield as an *E/Z* mixture in the geometry of the oxime ether group in 3:2 ratio.⁷ The amine **2** was protected with di-*tert*-butyl dicarbonate under the Schotten-Baumann type conditions to afford the *N*-Boc derivative **3** in 92% yield. Mild oxidation of **3** with chromium trioxide-pyridine provided the unstable aldehyde **4** in 63% yield in favor of the *E* isomer in 5:4 ratio.



Scheme 1. Reagents and conditions: a) 2-aminoethanol, rt, 88%. b) $(\text{Boc})_2\text{O}$, Na_2CO_3 , acetone, H_2O , reflux, 92%. c) CrO_3 -Py, CH_2Cl_2 , rt, 63%.

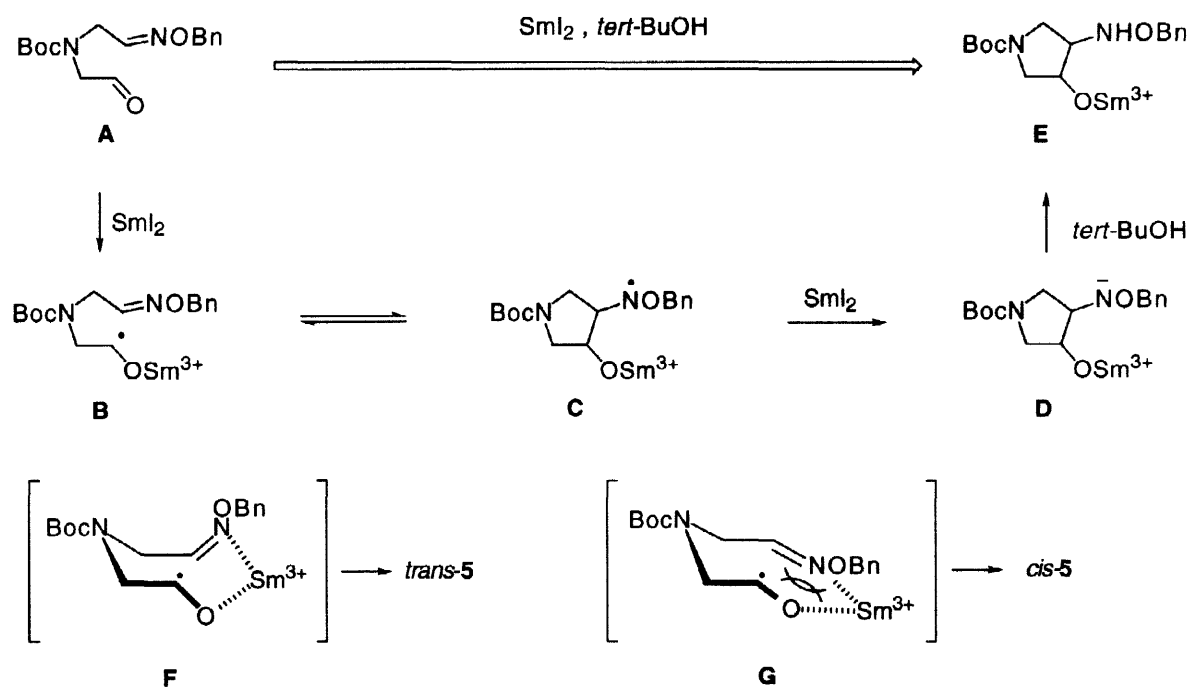
In order to improve the stereoselectivity in radical cyclization of **4** using stannyl radical,⁸ we investigated the intramolecular reductive coupling between the formyl and oxime ether groups in the aldehyde **4** based on the chemistry of SmI_2 (Table 1). This unique one-electron reducing agent has been recently used for the radical reaction with a high degree of chemo-, regio- and stereoselectivities.⁹ Treatment of an *E/Z* mixture of **4** with commercially available 0.1 M solution of SmI_2 in THF (3.0 equiv.) at 25 °C underwent smooth cyclization to give a 3:2 mixture of two cyclized products *trans*-**5** and *cis*-**5** in 33% combined yield in favor of *trans*-amino alcohol (entry 1).¹⁰ No reaction was observed in the absence of *tert*-BuOH, thus a proton donor such as *tert*-BuOH was found to be essential for SmI_2 -induced ring formation (entry 2). Each isomer could be easily separated by flash column chromatography and relative stereostructures were firmly established by the formation of the corresponding acetonide in *cis*-**5** while *trans*-**5** recovered completely under the same reaction conditions. The stereoselectivity and chemical yield were shown to be dependent on the reaction temperature, thus changing the temperature from 25 to -78 °C led to an effective increase in *trans/cis* selectivity to 9:1 and combined yield to 70%, better than that obtained by stannyl radical-promoted reaction (entry 3).⁸ Interestingly, this 5-*exo-trig* radical cyclization took place smoothly even in the absence of HMPA, in contrast to the analogous 7-*exo-trig* radical cyclization in our previous experiment.¹¹ A similar result has been recently reported by Chiara in reductive coupling of carbonyl-tethered oxime ethers for the synthesis of aminocyclopentitols.¹² The rationale of the reaction pathway of this reductive coupling reaction is that single-electron transferred to the formyl group to form a ketyl radical **B** which then attacked the oxime ether group (Scheme 2). In this reaction, the oxime

Table 1. SmI₂-induced cyclization of oxime ether 4


Entry	Additive	Temp. (°C)	Yield (%) ^a	Selectivity ^b
1	<i>tert</i> -BuOH	25	33	3 : 2
2	none	25	no reaction	—
3	<i>tert</i> -BuOH	-78	70	9 : 1

^aCombined yields of *trans*-5 and *cis*-5. ^bSelectivities are based on respective isolated yields of *trans*-5 and *cis*-5.

ether group acts as an excellent radical acceptors because of the extra stabilization of the intermediate aminyl radical C provided by the lone pair on the adjacent oxygen atom. The process was completed by SmI₂-induced reduction of the intermediate aminyl radical C followed by protonation of the resulting amide anion D by *tert*-BuOH. Therefore, a twofold excess of SmI₂ is theoretically necessary for the successful cyclization. The preferential formation of *trans*-5 could be explained by assuming both the electronic and steric repulsions between the ketyl radical moiety and the oxime ether group, as indicated in the transition states of the chairlike conformations F and G, of which the former F would be more stable than the latter G.

**Scheme 2.**

Synthesis of 4-pyrimidinyl- and 4-purinylypyrrolidin-3-ol nucleoside analogues

Modifications of nucleoside framework in which the furanose oxygen atom was replaced by another hetero atom have recently led to the discovery of a novel class of potential anticancer and antiviral agents.¹³ It is proposed that a slight change in the size and electronegativity of the hetero atom would lead to the compounds

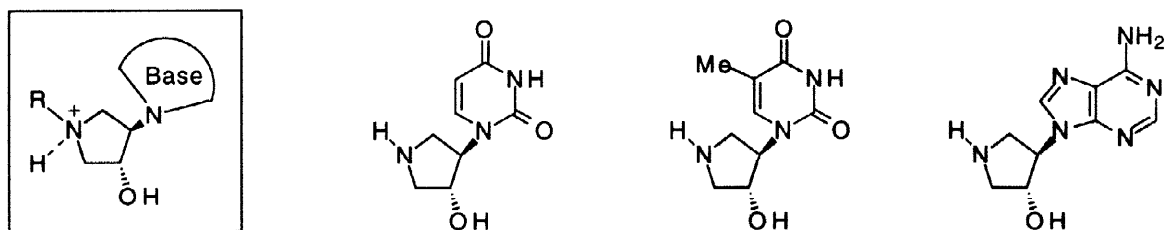
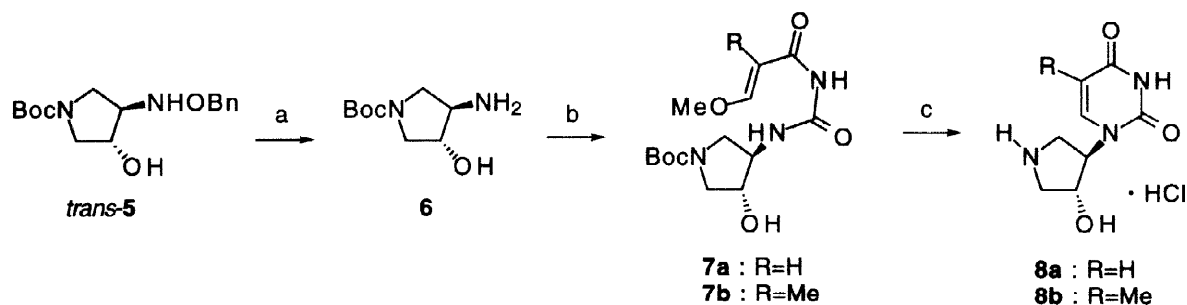


Figure 1. 4-Pyrimidinyl- and 4-purinylnucleoside analogues.

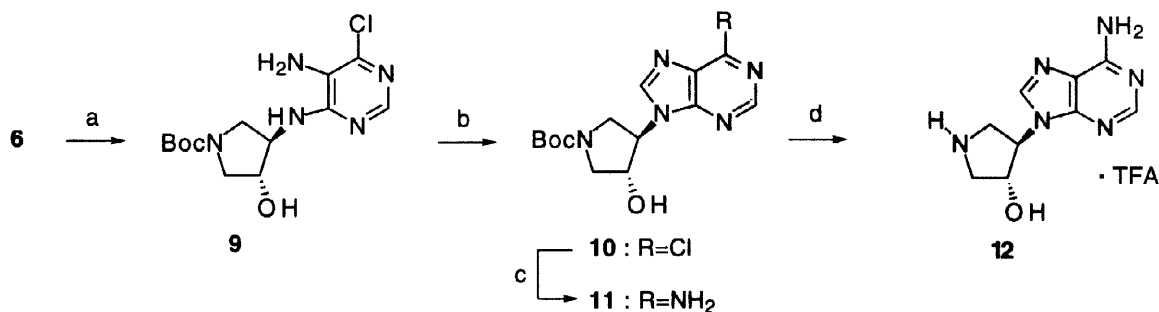
that would increase biological activity and metabolic stability and decrease the toxicity of 4'-oxo analogues. Since incorporation of a nitrogen atom into furanose ring has not been extensively investigated,¹⁴ we have started synthetic studies of a new class of 4-pyrimidinyl- and 4-purinylnucleoside analogues which may have wide-ranging therapeutic potential based on the following reasons (Figure 1). Replacement of the 4'-chiral carbon atom of a nucleoside by a nitrogen atom would provide the system with more conformational flexibility. Moreover, positive charge associated with protonation to the nitrogen atom on pyrrolidine ring would be expected to play an important role on the inhibition of viral or cellular enzymes which are essential for viral replication.¹⁵ Additionally, an amino functionality in these designed analogues can also allow ready access to introduction and modification of the substituent R on the nitrogen atom, thus leading to the formation of a variety of nucleoside analogues.

The synthesis of uridine, thymidine and adenosine analogues was achieved by the standard pyrimidine and purine rings construction method. Hydrogenolysis of the benzyloxyamino group in *trans*-**5** in the presence of platinum dioxide afforded the amino alcohol **6** in 76% yield which was then treated with the corresponding isocyanates¹⁶ in benzene-DMF at low temperature to give the acryloylureas **7a** and **7b** in 91 and 53% yields, respectively (Scheme 3). Acid-catalyzed cyclization of **7ab** gave the uridine and thymidine analogues **8ab** in high yields as a result of concomitant deprotection of the *N*-*tert*-butoxycarbonyl group.



Scheme 3. Reagents and conditions: a) H₂, PtO₂, MeOH, rt, 76%. b) 3-methoxyacryloyl isocyanate (for **7a**), 3-methoxy-2-methylacryloyl isocyanate (for **7b**), DMF, benzene, -20 °C - rt, 91% (**7a**) and 53% (**7b**). c) HCl, MeOH, rt, quant. (**8a**) and quant. (**8b**).

Refluxing a solution of a mixture of **6**, commercially available 5-amino-4,6-dichloropyrimidine and triethylamine in *n*-BuOH produced a common precursor **9** which was then subject to the reaction with diethoxymethyl acetate followed by treatment with *p*-TsOH in toluene to afford purine derivative **10** in 35% yield from **6** (Scheme 4). Treatment of **10** with methanolic ammonia in sealed tube at 120 °C gave a 95% yield of **11** which was then deprotected by treatment with trifluoroacetic acid to afford the desired adenosine analogue



Scheme 4. Reagents and conditions: a) 5-amino-4,6-dichloropyrimidine, triethylamine, *n*-BuOH, reflux. b) AcOCH(OEt)₂, reflux, and then *p*-TsOH, toluene, rt, 35% (from **6**). c) NH₃, MeOH, in sealed tube, 120 °C, 95%. d) TFA, CH₂Cl₂, rt, quant.

12 in almost quantitative yield. Evaluation of the biological activities of three products **8a**, **8b** and **12** thus prepared is now in progress.

CONCLUSION

We established 5-*exo-trig* radical cyclization of oxime ether connected with the formyl group by use of samarium diiodide, providing a powerful method for preparing 5-membered cyclic compounds bearing the hydroxyl and amino functional groups in good chemical yield with a high degree of stereoselectivity. The method was successfully applied to the synthesis of 4-pyrimidinyl- and 4-purinylylpyrrolidin-3-ol nucleoside analogues.

EXPERIMENTAL SECTION

General. ¹H NMR spectra were measured using Varian Gemini-200 (200 MHz), Varian Gemini-300 (300 MHz) and VXR-500 (500 MHz) instruments. ¹³C NMR spectra were measured using Varian Gemini-200 (50 MHz) and VXR-500 (125 MHz). IR spectra were measured with a Perkin Elmer 1600 FTIR machine and mass spectra were taken by Hitachi M-4100 spectrometer. Mps were determined with a Kofler-type hot-stage apparatus and are uncorrected. For flash column chromatography, E. Merck Kieselgel 60 (230-400 mesh) was used.

***N*-(2-Hydroxyethyl)aminoethanal *O*-Benzyloxime (**2**).** To 2-aminoethanol (10 ml, 166 mmol) was added chloroacetaldehyde *O*-benzyloxime **1**⁶ (10 g, 54.5 mmol) under a nitrogen atmosphere at 0 °C. After stirring at rt for 12 h, the reaction mixture was added to saturated aqueous NaHCO₃ and CH₂Cl₂. The layers were separated and the aqueous phase was extracted with CH₂Cl₂. The combined organic phase was washed with brine, dried over Na₂SO₄ and concentrated at reduced pressure. Purification of the residue by flash column chromatography (CHCl₃/MeOH 30:1 to CHCl₃/MeOH 15:1) afforded **2** (10 g, 88%) as colorless crystals and a 3:2 mixture of *E/Z*-oxime. mp 58.5–60 °C (AcOEt/hexane). IR (CHCl₃) 3600–3300 (OH, NH) cm⁻¹. ¹H NMR (CDCl₃) δ 7.49 (3/5H, t, *J*=5.2 Hz), 7.38–7.25 (5H, m), 6.79 (2/5H, t, *J*=4.4 Hz), 5.10 (4/5H, s), 5.07 (6/5H, s), 3.65–3.57 (2H, m), 3.56 (4/5H, d, *J*=4.4 Hz), 3.38 (6/5H, d, *J*=5.2 Hz), 2.78–2.70 (2H, m). ¹³C NMR (CDCl₃) δ 151.31, 149.00, 137.60, 137.37, 128.34, 128.16, 127.96, 127.84, 76.07,

75.77, 60.80, 60.71, 50.96, 50.62, 47.72, 44.41. HRMS: Calcd for $C_{11}H_{17}N_2O_2$ ($M+H^+$): 209.1289, Found: 209.1271. Anal. Calcd for $C_{11}H_{16}N_2O_2$: C, 63.44; H, 7.74; N, 13.45, Found: C, 63.43; H, 7.76; N, 13.50.

***N*-(*tert*-Butoxycarbonyl)-*N*-(2-hydroxyethyl)aminoethanal *O*-Benzoyloxime (3).** To a solution of **2** (4.0 g, 19.2 mmol) in acetone (60 ml) was added a solution of Na_2CO_3 (3.5 g, 33 mmol) in H_2O (15 ml) under a nitrogen atmosphere at rt. After di-*tert*-butyl dicarbonate (6.0 g, 28.8 mmol) was added dropwise at 0 °C, the reaction mixture was heated to reflux for 30 min. After the reaction mixture was filtered through a pad of Celite, the filtrate was concentrated at reduced pressure. The resulting residue was quenched with water and then extracted with CH_2Cl_2 . The organic phase was washed with brine, dried over Na_2SO_4 and concentrated at reduced pressure. Purification of the residue by flash column chromatography (AcOEt/hexane 1:2) afforded **3** (5.4 g, 92%) as a colorless oil and a 3:2 mixture of *E/Z*-oxime. The presence of rotamers precluded a comprehensive assignment of all proton and carbon resonances. IR ($CHCl_3$) 3435 (OH), 1689 (NCOO) cm^{-1} . 1H NMR ($CDCl_3$) δ 7.45 (3/5H, br m), 7.38–7.25 (5H, m), 6.74 (2/5H, br m), 5.11 (4/5H, s), 5.06 (6/5H, s), 4.2–4.1 (4/5H, br m), 4.0–3.9 (6/5H, br m), 3.67 (2H, br m), 3.37 (2H, br m), 1.45 (18/5H, s), 1.44 (27/5H, s). ^{13}C NMR ($CDCl_3$) δ 150.23, 147.88, 147.56, 137.48, 137.16, 128.31, 128.17, 127.94, 127.90, 127.84, 80.58, 76.12, 75.94, 61.46, 60.94, 50.73, 50.24, 47.36, 44.87, 28.22. HRMS: Calcd for $C_{16}H_{25}N_2O_4$ ($M+H^+$): 309.1812, Found: 309.1795.

***N*-(*tert*-Butoxycarbonyl)-*N*-(2-oxoethyl)aminoethanal *O*-Benzoyloxime (4).** To a solution of pyridine (15.7 ml, 195 mmol) in CH_2Cl_2 (250 ml) was portionwise added CrO_3 (9.74 g, 97.4 mmol) under a nitrogen atmosphere at rt. After stirring at rt for 15 min, a solution of **3** (5.0 g, 16.2 mmol) in CH_2Cl_2 (32 ml) was added to the reaction mixture. After the reaction mixture was stirred at the same temperature for 1.5 h, the solvent was evaporated at reduced pressure. After the resulting residue was diluted with Et_2O and filtered through a pad of Celite, the filtrate was concentrated at reduced pressure. Purification of the residue by flash column chromatography (AcOEt/hexane 1:3) afforded **4** (3.12 g, 63%) as a colorless oil and a 5:4 mixture of *E/Z*-oxime. The presence of rotamers precluded a comprehensive assignment of all proton and carbon resonances. IR ($CHCl_3$) 1736 (CHO), 1698 (NCOO) cm^{-1} . 1H NMR ($CDCl_3$) δ 9.51 (1H, br m), 7.41 (5/9H, t, $J=5.1$ Hz), 7.4–7.3 (5H, m), 6.82 (4/9H, t, $J=4.4$ Hz), 5.09 (8/9H, s), 5.05 (10/9H, s), 4.3–3.7 (4H, br m), 1.45 (36/9H, s), 1.42 (45/9H, s). ^{13}C NMR ($CDCl_3$) δ 198.18, 197.59, 149.30, 148.66, 146.04, 137.28, 137.20, 128.41, 128.21, 128.12, 127.99, 81.34, 76.27, 75.98, 58.21, 56.67, 47.40, 46.68, 44.79, 44.14, 28.09. HRMS: Calcd for $C_{16}H_{23}N_2O_4$ ($M+H^+$): 307.1656, Found: 307.1653.

Radical cyclization using Sml_2 . To a solution of **4** (153 mg, 0.5 mmol) and *tert*-BuOH (0.12 ml, 1.25 mmol) in THF (10 ml) was added dropwise Sml_2 (0.1 M in THF) (15 ml, 1.5 mmol) under an argon atmosphere at -78 °C. The reaction mixture was stirred at the same temperature for 30 min. After the solvent was evaporated at reduced pressure, the resulting residue was diluted with Et_2O and filtered through a pad of Celite. After the filtrate was concentrated at reduced pressure, purification of the residue by flash column chromatography (AcOEt/hexane 2:1) afforded *trans*-**5** (97 mg, 63%) and *cis*-**5** (11 mg, 7%) both as a colorless oil. The presence of rotamers precluded a comprehensive assignment of all proton and carbon resonances.

***trans*-4-(Benzyloxyamino)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-ol (*trans*-5).** IR (CHCl₃) 3600–3300 (OH, NH), 1675 (NCOO) cm⁻¹. ¹H NMR (CDCl₃) δ 7.4–7.3 (5H, m), 4.68 (2H, s), 4.23 (1H, br m), 3.65–3.55 (2H, br m), 3.53 (1H, br m), 3.3–3.1 (2H, br m), 1.45 (9H, s). ¹³C NMR (CDCl₃) δ 154.67, 137.27, 128.59, 128.47, 128.11, 79.62, 76.93, 72.61, 71.67, 66.45, 65.89, 51.91, 51.65, 47.44, 46.89, 28.44. HRMS: Calcd for C₁₆H₂₅N₂O₄ (M+H⁺): 309.1768, Found: 309.1788.

***cis*-4-(Benzyloxyamino)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-ol (*cis*-5).** IR (CHCl₃) 3600–3300 (OH, NH), 1689 (NCOO) cm⁻¹. ¹H NMR (CDCl₃) δ 7.4–7.3 (5H, m), 4.71 (2H, s), 4.25 (1H, br d, *J*=15.0 Hz), 3.7–3.4 (4H, br m), 3.04 (1H, br m), 1.44 (9H, s). ¹³C NMR (CDCl₃) δ 154.48, 137.20, 128.49, 128.17, 79.53, 76.57, 69.14, 68.37, 62.51, 61.82, 52.86, 52.58, 45.76, 45.07, 28.41. HRMS: Calcd for C₁₆H₂₄N₂O₄ (M⁺): 308.1734, Found: 308.1746.

***trans*-4-Amino-1-(*tert*-butoxycarbonyl)pyrrolidin-3-ol (6).** A suspension of PtO₂ (50 mg, 0.22 mmol) in MeOH (1 ml) was stirred under a hydrogen atmosphere at rt for 1 h. A solution of *trans*-5 (100 mg, 0.32 mmol) in MeOH (3 ml) was added to a resulting suspension. After stirring under a hydrogen atmosphere at rt for 12 h, the reaction mixture was filtered and the filtrate was concentrated at reduced pressure. Purification of the residue by flash column chromatography (AcOEt/hexane 1:1) afforded **6** (50 mg, 76%) as a white solid. The presence of rotamers precluded a comprehensive assignment of all proton and carbon resonances. IR (CHCl₃) 3600–3300 (OH, NH), 1690 (NCOO) cm⁻¹. ¹H NMR (CDCl₃) δ 3.98 (1H, br m), 3.69 (2H, br m), 3.29 (2H, br m), 3.10 (1H, br m), 1.46 (9H, s). ¹³C NMR (CDCl₃) δ 154.73, 79.60, 76.73, 76.20, 57.69, 57.11, 52.06, 51.67, 51.57, 51.32, 28.50. HRMS: Calcd for C₉H₁₈N₂O₃ (M⁺): 202.1316, Found: 202.1340.

***trans*-1-(*tert*-Butoxycarbonyl)-4-[(3-methoxy-1-oxo-2-propenyl)aminocarbonyl-amino]pyrrolidin-3-ol (7a).** To a solution of **6** (506 mg, 2.5 mmol) in DMF (3 ml) was added dropwise a solution of 3-methoxyacryloyl isocyanate¹⁶ (318 mg, 2.5 mmol) in benzene (3 ml) under a nitrogen atmosphere at -20 °C. After stirring at -15 °C for 1 hr, the reaction mixture was then stirred at rt for 18 h. After the solvent was evaporated at reduced pressure, the resulting residue was diluted with AcOEt. The organic phase was washed with water and brine, dried over Na₂SO₄ and concentrated at reduced pressure. Purification of the residue by flash column chromatography (CHCl₃/MeOH 30:1) afforded **7a** (747 mg, 91%) as a white powder. The presence of rotamers precluded a comprehensive assignment of all proton and carbon resonances. IR (CHCl₃) 3600–3200 (OH, NH), 1687 (CO) cm⁻¹. ¹H NMR (CDCl₃) δ 9.27 (1H, br m), 8.92 (1H, br m), 7.69 (1H, d, *J*=12.2 Hz), 5.30 (1H, d, *J*=12.2 Hz), 4.3–4.1 (2H, br m), 3.75 (3H, s), 3.9–3.65 (3H, br m), 3.4–3.2 (2H, br m), 1.46 (9H, s). ¹³C NMR (CDCl₃) δ 168.13, 164.15, 155.87, 154.43, 97.05, 79.92, 74.87, 74.04, 57.97, 56.72, 56.24, 51.40, 50.96, 49.19, 48.56, 28.38. HRMS: Calcd for C₁₄H₂₄N₃O₆ (M+H⁺): 330.1663, Found: 330.1666.

***trans*-1-(*tert*-Butoxycarbonyl)-4-[(3-methoxy-2-methyl-1-oxo-2-propenyl)-aminocarbonylamino]pyrrolidin-3-ol (7b).** Following the same procedure as for **7a**, compound **7b** was obtained from **6** and 3-methoxy-2-methylacryloyl isocyanate¹⁶ in 53% yield as a white powder. The

presence of rotamers precluded a comprehensive assignment of all proton and carbon resonances. IR (CHCl₃) 3600–3200 (OH, NH), 1688 (NCOO) cm⁻¹. ¹H NMR (DMSO-*d*₆) δ 9.82 (1H, br s), 8.74 (1H, br m), 7.47 (1H, br s), 5.42 (1H, br d, *J*=3.8 Hz), 4.1–3.9 (2H, br m), 3.80 (3H, s), 3.54 (1H, br m), 3.34 (1H, br m), 3.13 (2H, m), 1.61 (3H, s), 1.40 (9H, s). ¹³C NMR (DMSO-*d*₆) δ 169.94, 158.55, 153.92, 153.77, 106.98, 78.71, 72.87, 72.03, 61.22, 55.64, 54.87, 51.79, 51.42, 49.66, 49.28, 28.21, 8.86. HRMS: Calcd for C₁₅H₂₅N₃O₆ (M⁺): 343.1742, Found : 343.1746.

***trans*-4-(Uracil-1-yl)pyrrolidin-3-ol Hydrochloride (8a).** A solution of **7a** (300 mg, 0.91 mmol) in 2*N*-HCl (15 ml) was stirred at rt for 3 h. After the solvent was evaporated at reduced pressure, purification of the residue by washing with Et₂O afforded **8a** (180 mg, quant.) as a white powder. IR (Nujol) 3400–3200 (OH, NH), 1678 (CO) cm⁻¹. ¹H NMR (CD₃OD) δ 7.63 (1H, d, *J*=7.9 Hz), 5.71 (1H, d, *J*=7.9 Hz), 4.72 (1H, m), 4.54 (1H, m), 3.9–3.6 (2H, m), 3.55–3.2 (2H, m). ¹³C NMR (D₂O) δ 169.30, 154.72, 149.56, 104.95, 75.38, 70.20, 53.98, 49.17. HRMS: Calcd for C₈H₁₂N₃O₃ (M+H⁺): 198.0878, Found : 198.0871.

***trans*-4-(Thymin-1-yl)pyrrolidin-3-ol Hydrochloride (8b).** Following the same procedure as for **8a**, compound **8b** was obtained from **7b** in quantitative yield as a white powder. IR (Nujol) 3400–3200 (OH, NH), 1698 (CO) cm⁻¹. ¹H NMR (D₂O) δ 7.49 (1H, s), 4.84 (1H, m), 4.62 (1H, m), 4.0–3.7 (3H, m), 3.37 (1H, dd, *J*=12.5, 5.6 Hz), 1.85 (3H, s). ¹³C NMR (D₂O) δ 169.46, 154.76, 145.05, 114.08, 75.43, 69.47, 53.94, 49.19, 14.23. HRMS: Calcd for C₉H₁₄N₃O₃ (M+H⁺): 212.1034, Found : 212.1056.

***trans*-1-(*tert*-Butoxycarbonyl)-4-(6-chloro-9*H*-purin-9-yl)pyrrolidin-3-ol (10).** To a solution of **6** (162 mg, 0.8 mmol) in ⁿBuOH (4.4 ml) was added 5-amino-4,6-dichloropyrimidine (164 mg, 1.0 mmol) and triethylamine (0.9 ml) under a nitrogen atmosphere at rt. After stirring at 120 °C for 14 h, the solvent was evaporated at reduced pressure. After the resulting residue was diluted with Et₂O, a resulting powder was filtered to afford crude product **9**. A solution of **9** in diethoxymethyl acetate (15 ml) was stirred under a nitrogen atmosphere at 110 °C for 7 h. After the solvent was evaporated at reduced pressure, a solution of *p*-TsOH·H₂O (20 mg, 0.12 mmol) in toluene (30 ml) was added to the resulting residue under a nitrogen atmosphere at rt. After stirring at the same temperature for 2.5 h, the solvent was evaporated at reduced pressure. Purification of the residue by flash column chromatography (CHCl₃/MeOH 20:1) afforded **10** (95 mg, 35%) as colorless crystals. The presence of rotamers precluded a comprehensive assignment of all proton and carbon resonances. mp 195–196 °C (AcOEt/hexane). IR (Nujol) 3300 (OH), 1674 (NCOO) cm⁻¹. ¹H NMR (CD₃OD) δ 8.77 (1H, s), 8.55 (1H, s), 5.04 (1H, br m), 4.84 (1H, br m), 4.06 (1H, br m), 3.97 (1H, br m), 3.83 (1H, br m), 3.34 (1H, br m), 1.50 (9H, s). ¹³C NMR (CD₃OD) δ 153.31, 152.91, 151.54, 146.93, 132.81, 127.54, 81.69, 73.48, 72.84, 62.83, 62.31, 52.35, 51.82, 48.78, 48.24, 28.72. HRMS: Calcd for C₁₄H₁₉N₅O₃³⁵Cl (M+H⁺): 340.1175, Found : 340.1190. Anal. Calcd for C₁₄H₁₈N₅O₃Cl : C, 49.49; H, 5.34; N, 20.61; Cl, 10.43, Found : C, 49.36; H, 5.27; N, 20.54; Cl, 10.46.

***trans*-4-(Adenin-9-yl)-1-(*tert*-butoxycarbonyl)pyrrolidin-3-ol (11).** A solution of **10** (900 mg, 2.65 mmol) in saturated methanolic ammonia (25 ml) in sealed tube was heated at 120 °C for 3 days. After the solvent was evaporated at reduced pressure, purification of the residue by flash column chromatography (CHCl₃/MeOH 10:1) afforded **11** (806 mg, 95%) as a white powder. The presence of rotamers precluded a

comprehensive assignment of all proton and carbon resonances. IR (Nujol) 3600–3200 (OH, NH), 1694 (NCOO) cm^{-1} . ^1H NMR (CD_3OD) δ 8.23 (1H, s), 8.05 (1H, s), 5.0–4.7 (2H, br m), 4.1–3.7 (3H, br m), 3.35 (1H, br m), 1.51 (9H, s). ^{13}C NMR ($\text{DMSO-}d_6$) δ 156.26, 152.54, 149.72, 139.61, 119.30, 79.30, 79.03, 71.74, 70.94, 60.72, 59.49, 51.27, 50.81, 47.91, 47.44, 28.20. HRMS: Calcd for $\text{C}_{14}\text{H}_{20}\text{N}_6\text{O}_3$ (M^+): 320.1595, Found: 320.1606.

***trans*-4-(Adenin-9-yl)pyrrolidin-3-ol Trifluoroacetic acid (12).** To a solution of **11** (750 mg, 2.34 mmol) in CH_2Cl_2 (1.7 ml) was added TFA (1.7 ml) under a nitrogen atmosphere at rt. After stirring at the same temperature for 24 h, the solvent was evaporated at reduced pressure. Purification of the residue by washing with Et_2O afforded **12** (780 mg, quant.) as a white powder. IR (Nujol) 3600–3200 (OH, NH) cm^{-1} . ^1H NMR (D_2O) δ 8.37 (2H, br s), 5.26 (1H, br m), 4.81 (1H, br m), 4.08 (2H, m), 3.83 (1H, dd, $J=12.8$, 5.1 Hz), 3.49 (1H, dd, $J=12.8$, 3.2 Hz). ^{13}C NMR (D_2O) δ 152.90, 151.01, 147.31, 147.02, 142.80, 76.71, 64.60, 53.89, 49.72. HRMS: Calcd for $\text{C}_9\text{H}_{13}\text{N}_6\text{O}$ ($\text{M}+\text{H}^+$): 221.1168, Found: 221.1159.

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