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Design and Synthesis of Potent "Sulfur-Free" Transition State Analogue Inhibitors of 5′-Methylthioadenosine Nucleosidase and 5′-Methylthioadenosine Phosphorylase

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5′-Methylthioadenosine/*S*-adenosylhomocysteine nucleosidase (MTAN) is a dual substrate bacterial enzyme involved in *S*-adenosylmethionine (SAM) related quorum sensing pathways that regulates virulence in many bacterial species. MTANs from many bacteria are directly involved in the quorum sensing mechanism by regulating the synthesis of autoinducer molecules that are used by bacterial communities to communicate. In humans, 5′-methylthioadenosine phosphorylase (MTAP) is involved in polyamine biosynthesis as well as in purine and SAM salvage pathways and thus has been identified as an anticancer target. Previously we have described the synthesis and biological activity of several aza-*C*-nucleoside mimics with a sulfur atom at the 5′ position that are potent *E. coli* MTAN and human MTAP inhibitors. Because of the possibility that the sulfur may affect bioavailability, we were interested in synthesizing "sulfur-free" analogues. Herein we describe the preparation of a series of "sulfur-free" transition state analogue inhibitors of *E. coli* MTAN and human MTAP that have low nano- to picomolar dissociation constants and are potentially novel bacterial anti-infective and anticancer drug candidates.

Introduction

The determination of enzymatic transition states is a powerful technique used to provide information on both the geometric and electronic features of the transition state and thus provides a blueprint for putative enzyme inhibitors incorporating transition state features.[1] This process has been applied to a number of *N*-ribosyl transferases, including purine nucleoside phosphorylase (PNP[a]),[2] 5′-methylthioadenosine phosphorylase (MTAP),[3] and 5′-methylthioadenosine/*S*-adenosylhomocysteine nucleosidase (MTAN),[4−6] and has led to the development of extremely potent inhibitors that incorporate transition state features.[1,7−9]

MTAN is a dual substrate enzyme that is found in bacteria but not mammals and is involved in polyamine and *S*-adenosylmethionine (SAM) quorum sensing pathways. Many bacteria utilize quorum sensing signaling molecules known as autoinducers (AIs) to communicate with each other. The production and detection of AIs coordinate some gene expression and regulate processes beneficial to microbial communities. Quorum sensing is a potentially useful target for bacterial anti-infective agents, as it has been shown that several mutant bacterial strains defective in quorum sensing are less virulent,[10,11] and as inhibition of quorum sensing is nonlethal to bacteria, the potential for the development of resistance is reduced when compared to more traditional anti-infective agents.

MTAN is a major route for the metabolism of methylthioadenosine (MTA) and *S*-adenosylhomocysteine (SAH) in bacteria. MTA is a byproduct of the formation of the AI-1 family of autoinducers (acylhomoserine lactones, for example, hydroxybutanoyl-L-homoserine lactone) that are believed to be responsible for intraspecies communication.[12] MTAN subsequently catalyzes the hydrolysis of MTA to adenine and 5-methylthio-D-ribose, which in turn is recycled into SAM. The MTAN-catalyzed hydrolysis of SAH leads to *S*-ribosylhomocysteine (SRH) which is a biochemical precursor to AI-2, a family of AIs important in interspecies bacterial communications.[13] Thus, inhibition of MTAN is expected to cause the accumulation of MTA, resulting in product inhibition of AI-1 production, and directly block the formation of SRH, the precursor of AI-2.

Human MTAP effects phosphorolysis of MTA and is involved in polyamine biosynthesis and purine salvage pathways. MTA is a byproduct formed during the biosynthesis of the polyamines spermidine and spermine, which have an important role in growth-related processes.[14] MTAP is the only known enzyme involved in the recycling of MTA in humans, and it has been proposed that inhibition of MTAP could increase MTA concentration to cause feedback inhibition of polyamine biosynthesis resulting in potential antiproliferative activity, which has made MTAP a target for the design of novel anticancer drugs.[15,16] We have previously reported a variety of transition state inhibitors of MTAP, one of which is currently in preclinical trials for the treatment of head and neck tumors.[8,17]

The transition states for the hydrolysis of MTA by *Escherichia coli* MTAN and phosphorolysis of MTA by human MTAP have been solved using a combination of kinetic isotope effects and computational modeling. In the case of *E. coli* it has been shown

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[a] Abbreviations: AI, autoinducer; 9-DAA, 9-deazaadenine; DADMe, 5′-deaza-1′-aza-2′-deoxy-1′-(9-methylene); DIAD, diisopropyl azodicarboxylate; ImmA, immucillin-A; MT, methylthio; MTA, methylthioadenosine; MTAN, 5′-methylthioadenosine/*S*-adenosylhomocysteine nucleosidase; MTAP, 5′-methylthioadenosine phosphorylase; PNP, purine nucleoside phosphorylase; SAH, *S*-adenosylhomocysteine; SAM, *S*-adenosylmethionine; SRH, *S*-ribosylhomocysteine.

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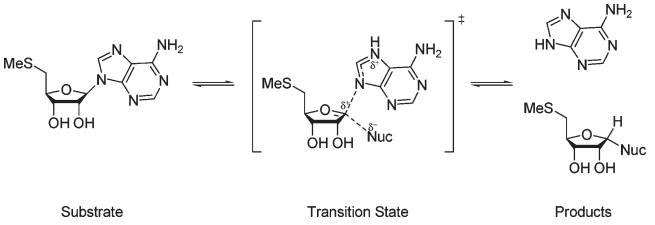


Figure 1. Reaction catalyzed by MTAP and MTANs with MTA as the substrate. In the case of MTAP the attacking nucleophile is phosphate, whereas in MTANs it is water.

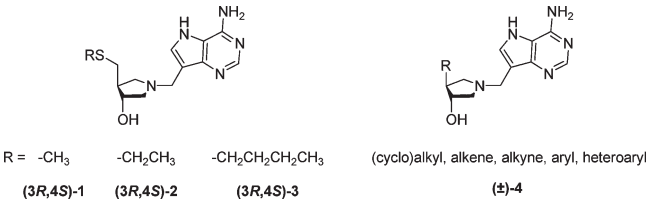


Figure 2. Known enantiopure transition state analogue inhibitors of MTANs (**3*R*,4*S*)-1**, (**3*R*,4*S*)-2**, and (**3*R*,4*S*)-3** and target racemic "sulfur-free" inhibitors (±)-**4**.

to have a late dissociative S_N1 transition state with extensive cleavage of the bond between adenine and the ribosyl moiety,[4] and for human MTAP it has been shown to be late dissociative S_N1 with a zero *N*-glycosidic bond order.[3] In MTAP the nucleophile responsible for the cleavage of the *N*-glycosidic bond is phosphate, while for *E. coli* MTAN the nucleophile is water (Figure 1).

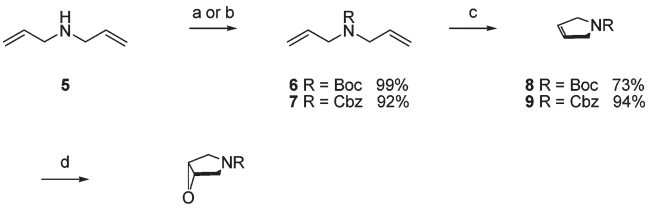
Previously we have reported the synthesis of potent transition state analogue inhibitors, based on a chiral 4-substituted-3-hydroxypyrrolidine motif, of which several exhibit binding affinities in the femtomolar range against *E. coli* MTAN and picomolar against MTAP.[18,19] Recently it has been shown that three of these compounds, MT-, EtT-, and BuT-DADMe-immucillin (**3*R*,4*S*)-1**, (**3*R*,4*S*)-2**, and (**3*R*,4*S*)-3**, respectively (Figure 2), disrupt AI production in *Vibrio cholerae* and *E. coli* and cause reduction in biofilm formation.[20]

In vivo screening of some of these chiral femtomolar inhibitors indicated that the sulfur atom may adversely affect bioavailability.[21] Herein we report the synthesis of a new family of transition state analogue inhibitors of MTAN and MTAP in which the sulfur atom has been removed. These racemic "sulfur-free" DADMe-immucillins (±)-**4** (Figure 2) have also been found to be potent inhibitors of the *E. coli* MTAN and human MTAP with dissociation constants in the low nano- to picomolar range and show potential as new anti-infective and anticancer drug candidates. These simplified inhibitors are easier and cheaper to prepare than the previously reported chiral compounds, and the removal of the sulfur atom may offer improved pharmacological properties.

Results and Discussion

Synthesis. Compounds (±)-**4** should be readily available by a Mannich reaction between a suitably substituted hydroxypyrrolidine, 9-DAA, and formaldehyde as described for the corresponding chiral immucillins.[22] Hydroxypyrrolidines of the type required for the racemic "sulfur-free" DADMe-immucillins (±)-**4** have been previously reported to be formed via the nucleophile opening of epoxypyrrolidines.[23,24] We decided to use a modification of the procedure described by Hansen and Bols,[23] as this would allow us to

Scheme 1[a]



[a] Reagents: (a) Boc_2O, MeOH, 0 °C; (b) benzyl chloroformate, Et_3N, CH_2Cl_2, 0 °C → room temperature; (c) $(PCy_3)_2Cl_2Ru{=}CHPh$, CH_2Cl_2, room temperature; (d) (i) NBS, DMSO, H_2O, room temperature, (ii) NaOH, MeOH, 0 °C → room temperature.

rapidly generate a series of hydroxypyrrolidines, via the addition of Grignard reagents to epoxides ***meso*-10** and ***meso*-11**. Diallylamine was protected as either its *tert*-butylcarbamate **6** or benzyloxycarbamate **7** and subjected to a ring closing metathesis reaction using Grubb's first generation catalyst.[25,26] Pyrrolines **8** and **9** were converted into the corresponding epoxides ***meso*-10** and ***meso*-11** via a two step bromohydrin/epoxidation sequence, in good yields (Scheme 1).

With the key epoxypyrrolidines in hand, ring-opening of the epoxide ring with various alkyl, cycloalkyl, and aryl Grignard reagents was investigated. Pyrrolidine subunits (±)-**20** − (±)-**22**, (±)-**24**, (±)-**26** were prepared by the copper(I) catalyzed addition of the corresponding Grignard reagent into epoxide ***meso*-11**, followed by hydrogenolysis of the N-protecting group. The deprotected amines were treated with formaldehyde and 9-DAA to afford the corresponding Mannich products (±)-**28** − (±)-**30**, (±)-**32**, and (±)-**34**. Compounds (±)-**15**, (±)-**17**, and (±)-**19** could not be isolated cleanly from the ring-opening reactions and were therefore used as crude compounds and purified after subsequent steps to generate immucillins (±)-**31**, (±)-**33**, and (±)-**35** (Scheme 2).

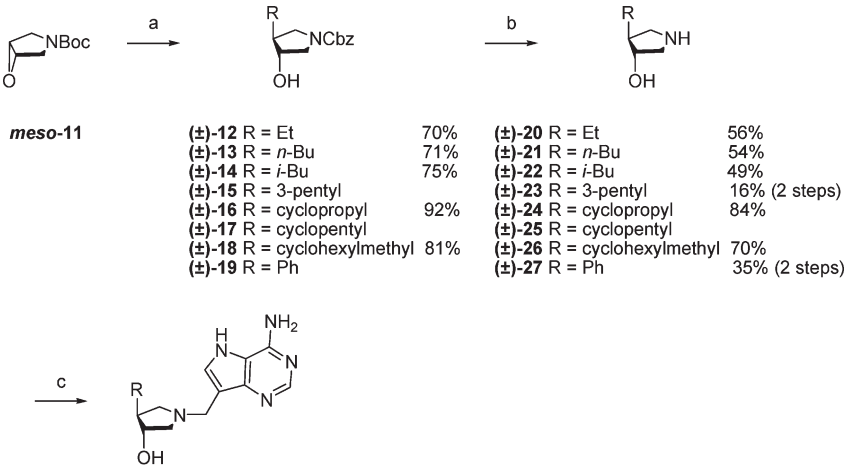
The vinyl and allyl-substituted DADMe-immucillins (±)-**40** and (±)-**41** were prepared in an analogous manner by addition of vinylmagnesium bromide or allylmagnesium chloride in the presence of copper(I) bromide dimethyl sulfide complex to *N*-Boc protected epoxide ***meso*-10** to give pyrrolidines (±)-**36** and (±)-**37**. Subsequent deprotection with 36% aqueous HCl in methanol afforded the corresponding pyrrolidine subunits (±)-**38** and (±)-**39**, which were coupled to 9-DAA to generate (±)-**40** and (±)-**41**, respectively (Scheme 3).

Ethynyl DADMe-immucillin (±)-**45** was synthesized in four steps from epoxide ***meso*-10**. Addition of trimethylsilylacetylene to ***meso*-10** in the presence of *n*-butyllithium and boron trifluoride etherate[27] gave (±)-**42**. Treatment with methanolic HCl gave (±)-**43**, which underwent a Mannich reaction with 9-DAA to give crude (±)-**44** which was directly deprotected under Zemplén conditions to give the desired DADMe-immucillin (±)-**45** after purification (Scheme 4).

Having prepared a series of alkyl, cycloalkyl, and aromatic substituted immucillins, we investigated what other biologically relevant substituents would be tolerated by the target enzymes, for example, 1,4-disubstituted 1-*H*-1,2,3-triazoles.[28]

Tsuzuki and co-workers reported the ring-opening of epoxide ***meso*-10** with sodium azide.[29] We repeated this and subjected the resulting azide (±)-**46** and trimethylsilylacetylene to the Sharpless copper(I) catalyzed azide−alkyne cycloaddition (CuAAC) conditions ($CuSO_4$, sodium ascorbate, *t*-BuOH, H_2O, room

Scheme 2[a]



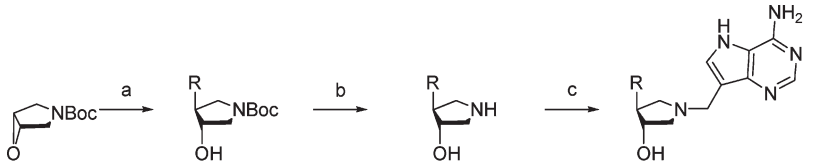
***meso*-11**

(±)-12 R = Et	70%	**(±)-20** R = Et	56%
(±)-13 R = *n*-Bu	71%	**(±)-21** R = *n*-Bu	54%
(±)-14 R = *i*-Bu	75%	**(±)-22** R = *i*-Bu	49%
(±)-15 R = 3-pentyl		**(±)-23** R = 3-pentyl	16% (2 steps)
(±)-16 R = cyclopropyl	92%	**(±)-24** R = cyclopropyl	84%
(±)-17 R = cyclopentyl		**(±)-25** R = cyclopentyl	
(±)-18 R = cyclohexylmethyl	81%	**(±)-26** R = cyclohexylmethyl	70%
(±)-19 R = Ph		**(±)-27** R = Ph	35% (2 steps)

(±)-28 R = Et	77%
(±)-29 R = *n*-Bu	47%
(±)-30 R = *i*-Bu	42%
(±)-31 R = 3-pentyl	33%
(±)-32 R = cyclopropyl	54%
(±)-33 R = cyclopentyl	10% (3 steps)
(±)-34 R = cyclohexylmethyl	46%
(±)-35 R = Ph	55%

[a] Reagents: (a) RMgX, CuBr·DMS, THF, −30 °C; (b) Pd (10 wt % on carbon), H_2, MeOH, room temperature; (c) formaldehyde, 9-DAA, 1,4-dioxane, H_2O, room temperature.

Scheme 3[a]

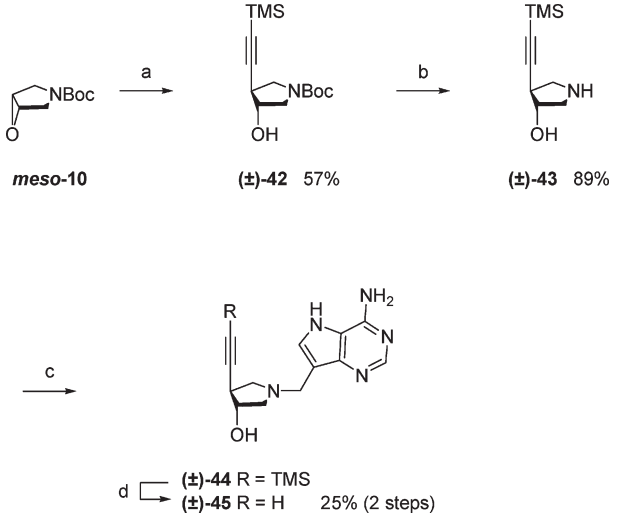


***meso*-10**

(±)-36 R = vinyl	75%	**(±)-38** R = vinyl	63%	**(±)-40** R = vinyl	57%
(±)-37 R = allyl	50%	**(±)-39** R = allyl	95%	**(±)-41** R = allyl	24%

[a] Reagents: (a) RMgX, CuBr·DMS, THF, −30 °C; (b) 36% aq HCl, MeOH, room temperature; (c) formaldehyde, 9-DAA, 1,4-dioxane, H_2O, room temperature.

Scheme 4[a]



***meso*-10** **(±)-42** 57% **(±)-43** 89%

[a] Reagents: (a) trimethylsilylacetylene, *n*-BuLi, $BF_3 \cdot OEt_2$, THF, −78 °C → room temperature; (b) 36% aq HCl, MeOH, room temperature; (c) formaldehyde, 9-DAA, 1,4-dioxane, H_2O, room temperature; (d) NaOMe, MeOH, room temperature.

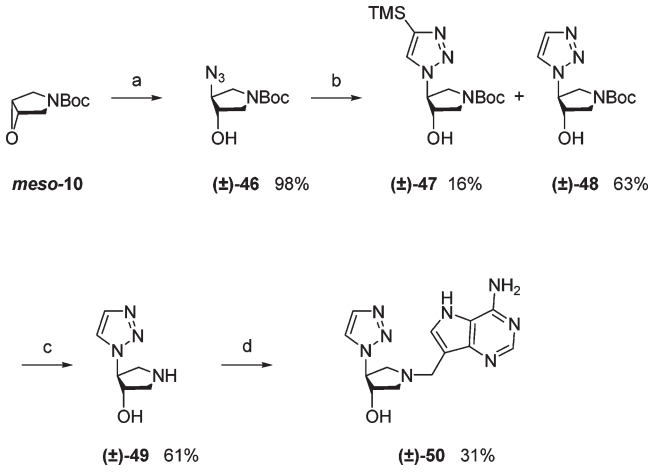
temperature),[30,31] but this was unsuccessful. However, the desired transformation could be achieved by simply refluxing the reagents in toluene. The crude mixture was treated with tetrabutylammonium fluoride to give TMS-triazole (±)-**47** and the desired desilylated triazole (±)-**48** in good yield. Removal of the nitrogen protecting group was achieved under our standard conditions (HCl/MeOH), and then pyrrolidine (±)-**49** was subjected to the Mannich reaction to afford DADMe-immucillin (±)-**50** (Scheme 5).

With ethynylpyrrolidine (±)-**42** in hand we attempted the formation of the *N*H-1,2,3-triazol-4-ylpyrrolidine subunit, an isomer of triazole subunit (±)-**48**. Selective removal of the TMS group in (±)-**42** with tetrabutylammonium fluoride gave (±)-**51**. Attempts to form the *N*H-1,2,3-triazol-4-yl compound from the resulting terminal alkyne present in (±)-**51** using recently reported methodology with either sodium azide[32] or "protected" azides[33] were unsuccessful. However, the N-substituted triazol-4-ylpyrrolidine (±)-**52** was prepared by reaction of (±)-**51** with benzylazide under Sharpless CuAAC conditions.[31] Removal of the Boc protecting group gave (±)-**53** which was coupled to 9-DAA using the standard Mannich conditions to afford (±)-**54** (Scheme 6).

As we had easy access to allylpyrrolidine (±)-**37**, we investigated the thiol−ene "click reaction".[34] Although counter to our

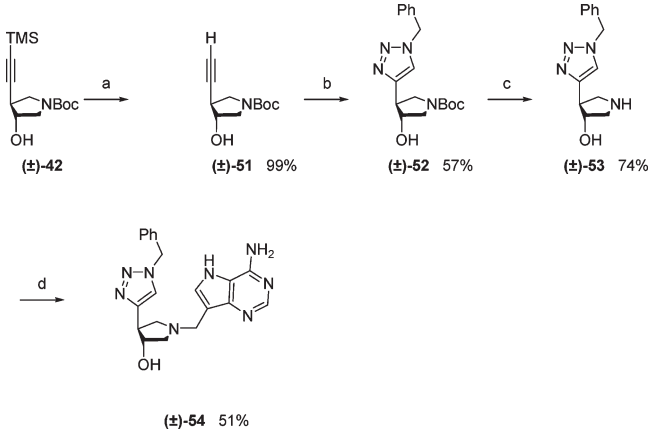
major objective of eliminating sulfur from our putative inhibitors, this reaction would allow us to probe the effect of increasing the length of the linker between the sulfur moiety and the pyrrolidine ring of the DADMe-immucillins and also demonstrate another synthetic strategy capable of generating large libraries of compounds via "click chemistry". Thus allylpyrrolidine (±)-**37** was treated with benzylmercaptan and 1,1′-azobis(cyanocyclohexane) in 1,4-dioxane at 90 °C[35] to give (±)-**55**. The crude product was treated with 36% aqueous HCl in methanol to afford (±)-**56**, which underwent a subsequent Mannich reaction to give the desired DADMe-immucillin (±)-**57** (Scheme 7).

Scheme 5[a]



[a] Reagents: (a) NaN_3, 1,4-dioxane, H_2O, 100 °C; (b) (i) trimethylsilylacetylene, toluene, 110 °C; (ii) TBAF (1 M in THF), THF, room temperature; (c) 36% aq HCl, MeOH; (d) formaldehyde, 9-DAA, 1,4-dioxane, H_2O, room temperature.

Scheme 6[a]

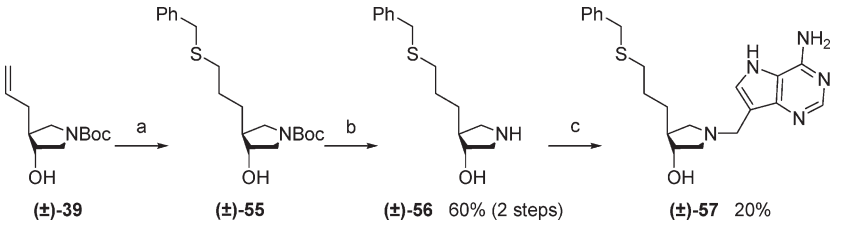


[a] Reagents: (a) TBAF (1 M in THF), THF, room temperature; (b) benzyl azide, sodium ascorbate, $CuSO_4$, *t*-BuOH, H_2O, room temperature; (c) 36% aq HCl, MeOH, room temperature; (d) formaldehyde, 9-DAA, 1,4-dioxane, H_2O, room temperature.

The use of copper salts to assist in the ring-opening of epoxides is known in some cases to give a mixture of the cis and the expected trans isomers;[23,36] thus, it was necessary to confirm the relative stereochemistry of our pyrrolidines. X-ray crystallography was not applicable, as none of the relevant intermediates or final DADMe-immucillin compounds were crystalline; therefore, known chiral amine (**3*R*,4*R*)-58**,[37] was converted into Et-DADMe-immucillin (**3*R*,4*S*)-69** via a modification of a previously reported route.[19] This provided material with known relative stereochemistry between the 3- and 4-position for direct comparison with the corresponding racemic compound (±)-**28**. Selective protection of the secondary hydroxyl group of amine (**3*R*,4*R*)-58** was achieved in three steps. Oxidation of the primary hydroxyl with Dess−Martin periodinane reagent gave aldehyde (**3*R*,4*S*)-62** which was methylenated under standard Wittig conditions. Hydrogenation of the olefinic group, followed by concomitant removal of both protecting groups, gave enantiopure amine (**3*R*,4*S*)-67**. A Mannich reaction with 9-DAA gave the enantiopure DADMe-immucillin (**3*R*,4*S*)-69**. As Bu-DADMe-immucillin (±)-**29** was the most potent racemic inhibitor of both *E. coli* MTAN and human MTAP, the same sequence was used to prepare enantiopure Bu-DADMe-immucillin (**3*R*,4*S*)-70** by substituting *n*-propyltriphenylphosphonium bromide as the Wittig reagent (Scheme 8).

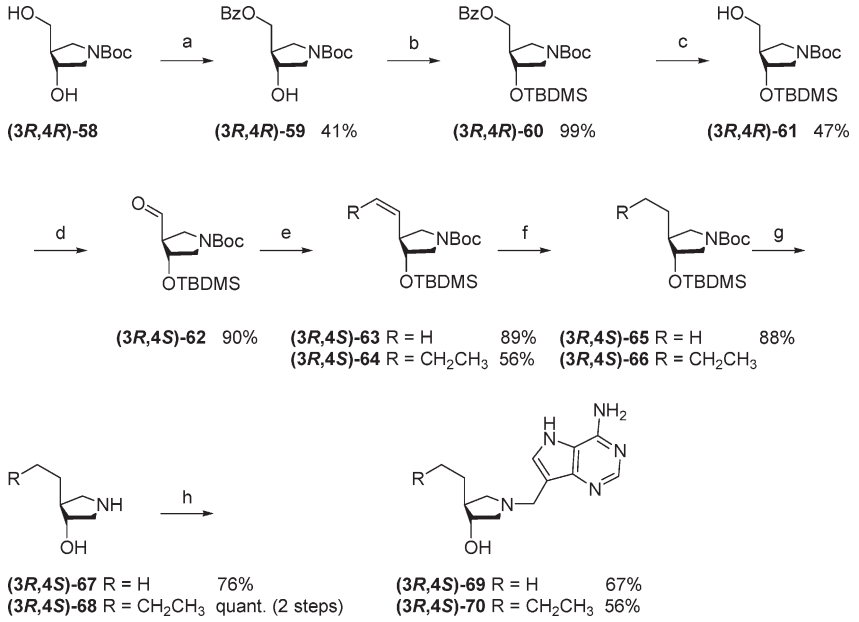
The ^1H and ^{13}C NMR data for enantiopure amine (**3*R*,4*S*)-67** and DADMe-immucillin (**3*R*,4*S*)-69** were identical to those of their racemic equivalents, compounds (±)-**20** and (±)-**28** respectively. To further confirm the relative stereochemical assignment of the C-3 and C-4 substituents in (±)-**20** and (±)-**28**, the hydroxyl group in pyrrolidine (±)-**12** was subjected to a Mitsunobu inversion protocol[38] by treatment with benzoic acid in the presence of DIAD and triphenylphosphine to give inverted ester (±)-**71** in good yield. Saponification of the benzoate followed by hydrogenation of the Cbz group gave pyrrolidine (±)-**73** which was converted into racemic *cis*-Et-DADMe-immucillin (±)-**74** (Scheme 9). Comparison of the NMR data of pyrrolidine *cis*-(±)-**73** with *trans*-(±)-**20** and (**3*R*,4*S*)-67** as well as DADMe-immucillin *cis*-(±)-**74** with *trans*-(±)-**28** and (**3*R*,4*S*)-69** showed clear differences. In particular the ^{13}C NMR resonance for C-3 in *trans*-Et-DADMe-immucillin (±)-**28** (77.7 ppm) was further downfield from that for the *cis* isomer (±)-**74** (72.5 ppm). All the DADMe-immucillins generated via the copper(I)-catalyzed Grignard ring-opening of epoxides ***meso*-10** or ***meso*-11** have the C-3 resonance between 76.7 and

Scheme 7[a]



[a] Reagents: (a) 1,1′-azobis(cyanocyclohexane), benzylmercaptan, 1,4-dioxane, 90 °C; (b) 36% aq HCl, MeOH, room temperature; (c) formaldehyde, 9-DAA, 1,4-dioxane, H_2O, room temperature.

Scheme 8[a]



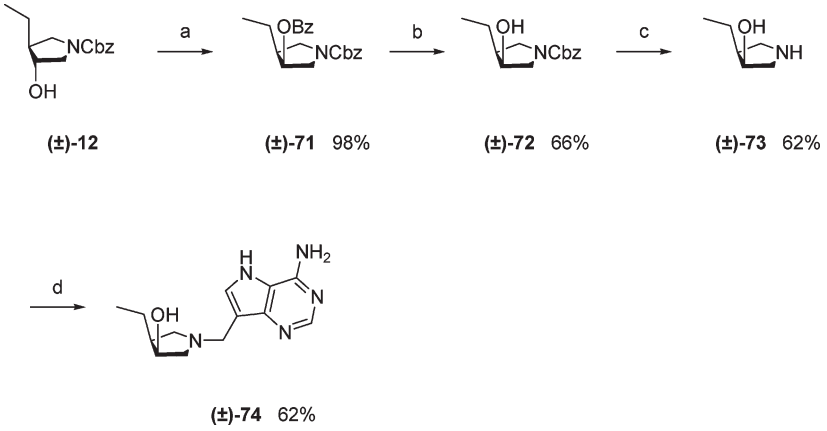
(3*R*,4*R*)-58 **(3*R*,4*R*)-59** 41% **(3*R*,4*R*)-60** 99% **(3*R*,4*R*)-61** 47%

(3*R*,4*S*)-62 90% **(3*R*,4*S*)-63** R = H 89% **(3*R*,4*S*)-64** R = CH_2CH_3 56% **(3*R*,4*S*)-65** R = H 88% **(3*R*,4*S*)-66** R = CH_2CH_3

(3*R*,4*S*)-67 R = H 76% **(3*R*,4*S*)-68** R = CH_2CH_3 quant. (2 steps) **(3*R*,4*S*)-69** R = H 67% **(3*R*,4*S*)-70** R = CH_2CH_3 56%

[a] Reagents: (a) $(Bu)_2SnO$, toluene, 110 °C, then BzCl, 5 °C → room temperature; (b) TBDMSCl, imidazole, DMF, room temperature; (c) NaOMe, MeOH, room temperature; (d) Dess−Martin periodinane, CH_2Cl_2, room temperature; (e) Ph_3PCH_3Br or $Ph_3PCH_2CH_2CH_3Br$, *n*-BuLi, THF, −78 °C → room temperature; (f) Pd (10 wt % on carbon) or $Pd(OH)_2$ (20 wt % on carbon), H_2 (1 atm), EtOH, room temperature; (g) TFA or 36% aq HCl in MeOH, room temperature; (h) formaldehyde, 9-DAA, 1,4-dioxane, H_2O, room temperature (for (**3*R*,4*S*)-69**) or 85 °C (for (**3*R*,4*S*)-70**).

Scheme 9[a]



(±)-12 **(±)-71** 98% **(±)-72** 66% **(±)-73** 62%

(±)-74 62%

[a] Reagents: (a) benzoic acid, DIAD, PPh_3, THF, 0 °C → room temperature; (b) K_2CO_3, EtOH, H_2O, 100 °C; (c) Pd (10 wt % on carbon), H_2, MeOH, room temperature; (d) formaldehyde, 9-DAA, 1,4-dioxane, H_2O, room temperature.

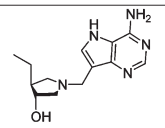
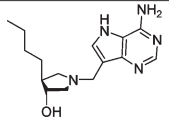
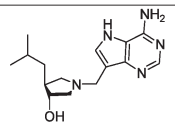
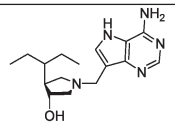
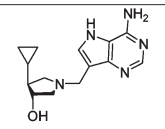
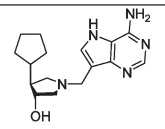
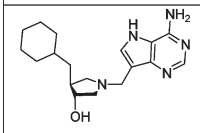
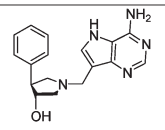
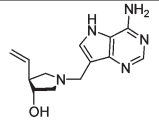
78.1 ppm, indicating a trans arrangement of substituents at C-3 and C-4.

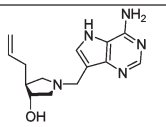
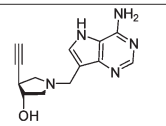
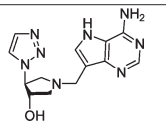
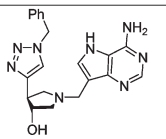
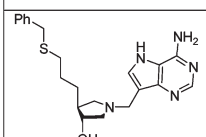
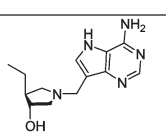
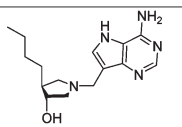
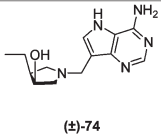
Inhibition Studies. The inhibition of *Escherichia coli* MTAN and human MTAP was evaluated with racemic immucillins (±)-**28** − (±)-**35**, (±)-**40**, (±)-**41**, (±)-**45**, (±)-**50**, (±)-**54**, (±)-**57**, and (±)-**74** and enantiopure immucillins (**3*R*,4*S*)-69** and (**3*R*,4*S*)-70** (Table 1).

E. coli MTAN showed broad tolerance for a variety of substituents in the C-4 position of the pyrrolidine ring and bound most of the compounds tightly with dissociation constants in the picomolar range. The diversity of functional groups accommodated at this position reaffirms the structural flexibility of the *E. coli* MTAN 5′ binding pocket.[9] The Bu-DADMe compound (±)-**29** gave the tightest binding (K_i* value of 9 pM) and was equivalent to its sulfur isostere (compound **2**, K_i* = 8 pM).[18] Thus, the presence of sulfur is not necessary for activity against *E. coli* MTAN. Shorter substituents (e.g., alkyl (±)-**28**, olefinic (±)-**40** and (±)-**41**, and alkynyl (±)-**45**) as well as the highly branched alkyl group (±)-**31** bound less well. The N-linked triazole group (±)-**50** (K_i = 2 nM) did not bind as well as the C-linked benzyl group (±)-**54** (K_i = 64 pM).

For human MTAP, Bu-DADMe-immucillin (±)-**29** was the best inhibitor in this family of compounds (K_i = 0.8 nM) with a comparable affinity to its sulfur-containing counterpart (K_i* = 1.4 nM), also suggesting that sulfur was not a necessary component of human MTAP inhibitors. Although MTAN prefers bulky substituents, human MTAP preferred the short alkyl and olefinic groups (±)-**28**, (±)-**40** and (±)-**41**. Comparisons of inhibitors for MTAN and MTAP are best made from the K_m/K_i ratio to provide comparative substrate and inhibitor interaction energies. For racemic Et-DADMe-immucillin (±)-**28**, the K_i values were 0.84 and 1.7 nM for *E. coli* MTAN and human MTAP, respectively. The respective

Table 1. Inhibition Constants for the Interaction of Immucillins with *E. coli* MTAN and Human MTAP[a] and the Ratio of the Two Values in Order To Provide a Qualitative Indication of the Therapeutic Window for the Treatment of an *E. coli* Infection

Compound	K_i for *E. coli* MTAN (nM)	K_i for Human MTAP (nM)	K_i Human MTAP / K_i *E. coli* MTAN
 **(±)-28**	0.84 ± 0.06	*3.2 ± 0.2	4
 **(±)-29**	*0.009 ± 0.001	0.8 ± 0.1	89
 **(±)-30**	*0.047 ± 0.009	*1.7 ± 0.3	36
 **(±)-31**	0.7 ±0.1	18 ± 2	26
 **(±)-32**	0.063 ± 0.005	*2.1 ± 0.3	33
 **(±)-33**	*0.013 ± 0.001	*2.6 ± 0.4	200
 **(±)-34**	0.059 ± 0.008	14 ± 2	237
 **(±)-35**	*0.03 ± 0.002	8 ± 1	267
 **(±)-40**	0.65 ± 0.03	3.2 ± 0.4	4.9

Compound	K_i for *E. coli* MTAN (nM)	K_i for Human MTAP (nM)	K_i Human MTAP / K_i *E. coli* MTAN
 **(±)-41**	0.35 ± 0.03	3.0 ± 0.3	8.6
 **(±)-45**	0.39 ± 0.02	31 ± 3	80
 **(±)-50**	2.0 ± 0.2	59 ± 8	30
 **(±)-54**	*0.064 + 0.005	-[b]	selective
 **(±)-57**	*0.054 ± 0.005	71 ± 5	1314
 **(3*R*,4*S*)-69**	0.31 ± 0.02	*0.7 ± 0.2	2
 **(3*R*,4*S*)-70**	0.0034 ± 0.0009	*0.55 ± 0.07	162
 **(±)-74**	1.8 ± 0.3	34 ± 3	19

[a] K_i is the dissociation constant for the first step in E + I ↔ EI ↔ EI*, the two-step binding characteristic of slow-onset tight-binding inhibition. ∗ indicates slow onset binding and is the overall dissociation constant for E + I ↔ EI*. In cases where no ∗ is shown, then slow-onset inhibition was not observed. [b] (−) Indicates that no inhibition was observed at 2.5 μM.

K_m/K_i ratios are 512 and 3105 for *E. coli* MTAN and human MTAP. Thus, the inhibitor is a better competitor for the catalytic site of human MTAP than for *E. coli* MTAN by a factor of 6. The same is true for inhibitors with short olefinic groups (±)**-40** and (±)**-41**. For (±)**-40**, the K_m/K_i ratios are 662 and 1649, while they are 1228 and 1759 for (±)**-41**, favored more by human MTAP than by *E. coli* MTAN. For the rest of the inhibitors, the K_m/K_i ratio suggests that *E. coli* MTAN has a higher affinity for these compounds relative to substrate than does human MTAP.

Single enantiomers are usually more potent than racemic mixtures,[39] as is the case for the inhibition constants for compounds (**3*R*,4*S*)-69** and (±)**-28** and (**3*R*,4*S*)-70** and (±)**-29** with *E. coli* MTAN and human MTAP. Likewise, the *trans*-Et-DADMe-immucillin (±)**-28** is a better inhibitor of both *E. coli* MTAN and human MTAP than *cis*-Et-DADMe-immucillin (±)**-74** which confirms that the trans stereochemistry is preferred as a transition state analogue.

DADMe-immucillin (±)**-57** is a relatively potent inhibitor of bacterial MTAN; however, increasing the linker between the benzyl thiol moiety and the pyrrolidine ring from one carbon (K_i^* = 0.5 pM)[18] to three carbons as in (±)**-57** (K_i^* = 54 pM) is detrimental to activity against *E. coli* MTAN. Although a similar reduction in activity against human MTAP was also observed, the magnitude of the K_m/K_i ratio of (±)**-57** (7963 for MTAN vs 74 for MTAP) reveals that this is one of the more selective inhibitors for the bacterial enzyme.

In terms of a therapeutic window a highly selective bacterial MTAN inhibitor is the benzyltriazole compound (±)**-54** which inhibited *E. coli* MTAN with a K_i^* of 64 pM without inhibiting human MTAP even at 2.5 μM. Interestingly, the N-linked triazole compound (±)**-50** was a weaker inhibitor than (±)**-54** for the bacterial enzyme but a better inhibitor for human MTAP. Again, this suggests that the *E. coli* enzyme 5′-binding pocket is able to accommodate bulkier aromatic groups much better than its human orthologue or better than other MTAN isozymes.[9] Exploiting these enzymatic subtleties may prove useful in designing clinically selective antibacterials.

Conclusions

A series of "sulfur-free" transition state analogues of *E. coli* MTAN and human MTAP have been designed and synthesized on the basis of their dissociative transition state structures. These racemic compounds can be rapidly prepared in a simple manner. We have demonstrated that the removal of the sulfur moiety from the transition state analogues is not detrimental to their activity against these enzymes. Further investigation into the bioavailability and other pharmacological properties of these potent "sulfur-free" inhibitors will be conducted and reported in due course.

Experimental Section

General. NMR spectra were recorded on a Bruker Avance III spectrometer at 500 MHz (^{1}H) or 125 MHz (^{13}C). Spectra were measured in either $CDCl_3$ or CD_3OD using Me_4Si as internal reference. High resolution accurate mass determinations were performed on a Waters Q-Tof Premier mass spectrometer under electrospray ionization conditions. Analytical HPLC was performed on an Agilent 1100 instrument, eluting with 0.1% w/w TFA in H_2O/MeOH gradient through a Phenomenex Synergi 4 μm polar-RP 80A, 250 mm × 4.6 mm column. Preparative HPLC was performed using a Gilson 321 pump, eluting 0.1% w/w TFA in H_2O/MeOH gradient through a Phenomenex Synergi 4 μm polar-RP 80A, 250 mm × 30 mm column and Agilent 1100 photodiode array detector. Thin layer chromatography was performed on glass-backed silica gel plates (Merck). Column chromatography was performed on silica gel (Davisil LC60A 40−63 μm). Anhydrous solvents were obtained from Aldrich. Methyltriphenylphosphonium bromide was azeotropically dried with toluene and stored in vacuo over P_2O_5 prior to use. All other reagents were used as received. All final compounds had a purity of >95% as assessed by analytical HPLC.

Chemistry. *tert*-Butyl Diallylcarbamate (6).[25] Di-*tert*-butyl dicarbonate (42.2 g, 193 mmol) was added, portionwise, to a solution of diallylamine (20 mL, 162 mmol) in methanol (500 mL) at 0 °C. After complete addition the reaction mixture was allowed to warm to room temperature, stirred for 1 h, then concentrated under reduced pressure. Dry flash chromatography of the residue (gradient 0−50% EtOAc in Petrol) afforded **6** as a colorless oil (31.9 g, 99%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.80−5.72 (m, 2H), 5.13−5.09 (m, 4H), 3.80 (br s, 4H), and 1.45 ppm (s, 9H).

***tert*-Butyl 3-Pyrroline-1-carboxylate (8).**[23] Grubb's first generation catalyst (920 mg, 1.1 mmol) was added to a solution of *tert*-butyl diallylcarbamate (**6**) (31.9 g, 162 mmol) in CH_2Cl_2 (370 mL). The reaction mixture was stirred for 17 h and then concentrated under reduced pressure. Dry flash chromatography of the residue (gradient: 0−70% EtOAc in Petrol) afforded **8** as a pale yellow oil (19.9 g, 73%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.80−5.74 (m, 2 H), 4.14−4.08 (m, 4H), and 1.48 ppm (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.3, 125.9, 125.8, 79.3, 53.1, 52.8 (rotamers), and 28.5 ppm. ESI-HRMS for $C_9H_{15}NONa$ $[MNa]^+$ calcd, 192.1000; found, 192.0997.

***tert*-Butyl 3,4-Epoxypyrrolidine-1-carboxylate (*meso*-10).**[23] *N*-Bromosuccinimide (8.05 g, 45 mmol) was added portionwise over 10 min to a solution of olefin (**8**) (6.4 g, 38 mmol) in DMSO (40 mL) and water (2 mL) at 0 °C. The reaction mixture was warmed to room temperature, stirred for 2.5 h, and then further *N*-bromosuccinimide (2 g, 11 mmol) was added. After the mixture was stirred for a further 2 h, the reaction was quenched by the addition of water (50 mL) and then extracted into EtOAc (4 × 50 mL). The combined organic phase was washed with brine (2 × 50 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was dissolved in MeOH (100 mL), cooled to 0 °C, and then an aqueous solution of NaOH (23 mL, 46 mmol, 2 M) was added in one portion. The mixture was warmed to room temperature, stirred for 17.5 h, and then the MeOH was removed under reduced pressure. The residue was partitioned between water (100 mL) and EtOAc (100 mL) and extracted with EtOAc (3 × 100 mL). The combined organic phase was washed with brine (2 × 100 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Flash chromatography of the residue (1:9 then 2:8, EtOAc/Petrol) afforded ***meso*-10** as a pale yellow oil (4.54 g, 64% over the two steps). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.81 (d, J = 12.9 Hz, 1H), 3.74 (d, J = 12.8 Hz, 1H), 3.66 (d, J = 5.3 Hz, 2H), 3.31 (dd, J = 12.6, 6.2 Hz, 2H), and 1.44 ppm (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.8, 79.8, 55.6, 55.1 (rotamers), 47.3, 46.9 (rotamers), and 28.4 ppm. ESI-HRMS for $C_9H_{15}NO_3Na$ $[MNa]^+$ calcd, 208.0950; found, 208.0955.

Benzyl Diallylcarbamate (7).[26] A solution of diallylamine (15 mL, 120 mmol) in CH_2Cl_2 (150 mL) was cooled to 0 °C, and Et_3N (23 mL, 160 mmol) and then benzyl chloroformate (20 mL, 140 mmol) were added dropwise. The reaction mixture was slowly allowed to warm to room temperature and stirred for 16 h and then quenched with water (200 mL). The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 200 mL). The combined organic phase was washed with brine (200 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Flash chromatography (gradient: 2−10% EtOAc in Petrol) of the residue afforded **7** as a pale yellow oil (25.9 g, 92%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35−7.29

(m, 5H), 5.77 (br s, 2H), 5.17−5.13 (br m, 6H), and 3.88 ppm (br s, 4H).

Benzyl 3-Pyrroline-1-carboxylate (9).[26] Grubb's first generation catalyst (173 mg, 0.21 mmol) was added to a solution of benzyl diallylcarbamate (**7**) (6.78 g, 29 mmol) in CH_2Cl_2 (300 mL). The reaction mixture was stirred for 16 h, and then further catalyst was added (340 mg, 0.4 mmol). The reaction mixture was stirred for a further 16 h and then concentrated under reduced pressure. Flash chromatography (1:9 then 2:8, EtOAc/Petrol) afforded **9** as a yellow oil (5.74 g, 94%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.39−7.29 (m, 5 H), 5.82−5.80 (m, 1H), 5.77−5.75 (m, 1H), 5.17 (s, 2H), and 4.22−4.18 ppm (m, 4H).

Benzyl 3,4-Epoxypyrrolidine-1-carboxylate (*meso*-11).[26] *N*-Bromosuccinimide (5.47 g, 31 mmol) was added to a solution of olefin (**9**) (5.02 g, 25 mmol) in DMSO (65 mL) and water (3.4 mL) at 0 °C. The reaction mixture was warmed to room temperature, stirred for 1.5 h, and then further *N*-bromosuccinimide (1.1 g, 6.2 mmol) was added. After the mixture was stirred for a further 3.5 h, the reaction was quenched by the addition of water (150 mL) and then extracted into EtOAc (3 × 150 mL). The combined organic phase was washed with brine (3 × 100 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was dissolved in MeOH (80 mL), cooled to 0 °C, and then an aqueous solution of NaOH (37 mL, 37 mmol, 1 M) was added in one portion. The mixture was warmed to room temperature, stirred for 5 h, then the MeOH was removed under reduced pressure. The residue was diluted with water (100 mL) and extracted with EtOAc (3 × 200 mL). The combined organic phases were washed with brine (200 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Flash chromatography of the residue (3:7 then 4:6, EtOAc/Petrol) afforded ***meso*-11** as a pale yellow oil (3.69 g, 68% over the two steps). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35−7.30 (m, 5H), 5.11 (dd, J = 17.9, 12.4 Hz, 2H), 3.87 (dd, J = 25.0, 12.9 Hz, 2H), 3.68 (d, J = 5.1 Hz, 2H), and 3.39 ppm (ddd, J = 12.8, 7.6, 0.8 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.3, 136.6, 128.5, 128.0, 127.9, 67.0, 55.5, 54.9 (rotamers), 47.5 and 47.2 (rotamers) ppm. ESI-HRMS for $C_{12}H_{13}NO_3Na$ $[MNa]^+$ calcd, 242.0793; found, 242.0791.

(±)-Benzyl *trans*-4-Ethyl-3-hydroxypyrrolidine-1-carboxylate [(±)-12]. A solution of epoxide (***meso*-11**) (467 mg, 2.13 mmol) and CuBr·DMS (53 mg, 0.26 mmol) in THF (20 mL) was cooled to −30 °C. Ethylmagnesium bromide (10 mL, 10 mmol, 1 M solution in THF) was added dropwise over 20 min, keeping the internal temperature below −30 °C. After complete addition the mixture was allowed to warm to −15 °C over 50 min and then quenched with 10% aqueous NH_4Cl solution (20 mL) and EtOAc (40 mL). The mixture was stirred at room temperature for 45 min, and then the layers were separated. The aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Flash chromatography of the residue (3:7 then 4:6, EtOAc/Petrol) afforded (±)-**12** as a pale yellow oil (370 mg, 70%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35−7.28 (m, 5H), 5.11 (s, 2H), 3.99 (br s, 1H,), 3.69−3.60 (m, 2H), 3.29 (td, J = 11.3, 4.1 Hz, 1H), 3.16−3.08 (m, 2H), 1.99−1.92 (m, 1H), 1.53−1.47 (m, 1H), 1.24−1.17 (m, 1H), and 0.93 ppm (dd, J = 12.4, 7.3 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.3, 136.9, 128.5, 128.0, 127.9, 67.0, 66.9 (rotamers), 53.1, 52.7 (rotamers), 49.4, 49.2 (rotamers), 48.0, 47.4 (rotamers), 24.4, and 12.3 ppm. ESI-HRMS for $C_{14}H_{19}NO_3Na$ $[MNa]^+$ calcd, 272.1263; found, 272.1269.

(±)-*trans*-4-Ethyl-3-hydroxypyrrolidine [(±)-20]. Palladium (20 mg, 0.02 mmol, 10 wt % on carbon) was added to a solution of (±)-**12** (270 mg, 1.1 mmol) in MeOH (10 mL) under argon. The reaction mixture was placed under a hydrogen atmosphere and stirred for 1 h and then filtered through Celite and concentrated under reduced pressure. Flash chromatography of the residue (5:4:1, CH_2Cl_2/MeOH/28% aqueous NH_4OH) afforded (±)-**20** as a yellow oil (70 mg, 56%). ^{1}H NMR (500 MHz, CD_3OD): δ = 3.94−3.91 (m, 1H), 3.23−3.19 (m, 1H), 2.98−2.95 (m, 1H), 2.78−2.76 (m, 1H), 2.51−2.47 (m, 1H), 1.87−1.81 (m, 1H), 1.54−1.46 (m, 1H), 1.32−1.23 (m, 1H), and 0.96 ppm (t, J = 7.4, 3H). ^{13}C NMR (125 MHz, CD_3OD): δ = 78.1, 54.7, 51.6, 51.0, 26.3, and 12.9 ppm. ESI-HRMS for $C_6H_{14}NO$ $[MH]^+$ calcd, 116.1075; found, 116.1070.

(±)-*trans*-1-[(9-Deazaadenin-9-yl)methyl]-4-ethyl-3-hydroxypyrrolidine [(±)-28]. Formaldehyde (120 μL, 1.5 mmol, 37 wt % solution in water) followed by 9-deazaadenine (102 mg, 0.9 mmol) was added to a solution of (±)-**20** (116 mg, 0.87 mmol) in 1,4-dioxane (1.6 mL) and water (3.2 mL). The reaction mixture was stirred at room temperature for 15 h, absorbed onto silica, and eluted down a silica column using a gradient 5−30% (7 N NH_3 in MeOH) in CH_2Cl_2. The crude product was collected, concentrated, and subjected to flash chromatography (5:4.9:0.1 then 5:4.8:0.2, CH_2Cl_2/MeOH/28% aqueous NH_4OH) to afford (±)-**28** as a pale yellow solid (175 mg, 77%). ^{1}H NMR (500 MHz, CD_3OD): δ = 8.16 (s, 1H), 7.49 (s, 1H), 3.87−3.78 (m, 3H), 3.07 (dd, J = 9.6, 8.1 Hz, 1H), 2.76 (dd, J = 10.4, 6.3 Hz, 1H), 2.70 (dd, J = 10.4, 4.0 Hz, 1H), 2.19 (dd, J = 9.7, 7.9 Hz, 1H), 1.91−1.84 (m, 1H), 1.59−1.50 (m, 1H), 1.38−1.28 (m, 1H), and 0.92 ppm (t, J = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, CD_3OD): δ = 152.1, 151.0, 147.0, 130.1, 115.1, 112.5, 77.4, 62.4, 59.4, 50.4, 49.1, 27.1, and 12.9 ppm; ESI-HRMS for $C_{13}H_{20}N_5O$ $[MH]^+$ calcd, 262.1668; found, 262.1664.

(±)-Benzyl *trans*-4-Butyl-3-hydroxypyrrolidine-1-carboxylate [(±)-13]. A solution of epoxide (***meso*-11**) (80 mg, 0.4 mmol) and CuBr·DMS (7 mg, 0.03 mmol) in THF (3 mL) was cooled to −30 °C. *n*-Butylmagnesium chloride (1 mL, 2 mmol, 2 M solution in THF) was added dropwise over 10 min, keeping the internal temperature below −25 °C. After complete addition the mixture was allowed to warm to −15 °C over 45 min and then quenched with 10% aqueous NH_4Cl solution (10 mL) and EtOAc (20 mL). The mixture was stirred at room temperature for 75 min, and then the layers were separated. The aqueous phase was extracted with EtOAc (2 × 20 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Flash chromatography of the residue (4:6 then 1:1, EtOAc/Petrol) afforded (±)-**13** as a pale yellow oil (72 mg, 71%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38−7.32 (m, 5H), 5.13 (s, 2H) 4.06−4.03 (m, 1H), 3.70−3.65 (m, 2H), 3.34−3.27 (m, 1H), 3.19−3.12 (m, 1H), 2.08−1.98 (m, 1H), 1.64 (br s, 1H), 1.51−1.44 (m, 1H), 1.36−1.15 (m, 5H), and 0.91−0.88 ppm (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.1, 136.8, 128.5, 127.9, 127.8, 75.4, 74.6 (rotamers), 66.8, 53.0, 52.6 (rotamers), 49.6, 49.4 (rotamers), 46.2, 45.7 (rotamers), 31.2, 29.9, 29.7(rotamers), 22.7, and 13.9 ppm. ESI-HRMS for $C_{16}H_{23}NO_3Na$ $[MNa]^+$ calcd, 300.1576; found, 300.1584.

(±)-*trans*-4-Butyl-3-hydroxypyrrolidine [(±)-21]. Palladium (10 mg, 0.01 mmol, 10 wt % on carbon) was added to a solution of (±)-**13** (70 mg, 0.3 mmol) in MeOH (4 mL) under argon. The reaction mixture was placed under a hydrogen atmosphere and stirred for 1.5 h and then filtered through Celite and concentrated under reduced pressure. Flash chromatography of the residue (5:4.8:0.2 then 5:4.5:0.5, CH_2Cl_2/MeOH/28% aqueous NH_4OH) afforded (±)-**21** as a yellow oil (20 mg, 54%). ^{1}H NMR (500 MHz, CD_3OD): δ = 4.19−4.17 (m, 1H), 3.55 (dd, J = 11.7, 7.3 Hz, 1H), 3.41 (dd, J = 12.3, 5.1 Hz, 1H), 3.16 (dd, J = 12.3, 3.1 Hz, 1H), 3.02 (dd, J = 11.7, 5.8 Hz, 1H), 2.23−2.17 (m, 1H), 1.55−1.49 (m, 1H), 1.40−1.28 (m, 5H) and 0.95−0.92 ppm (m, 3H). ^{13}C NMR (125 MHz, CD_3OD): δ = 75.3, 52.4, 50.0, 47.3, 31.9, 31.0, 23.6, and 14.3 ppm. ESI-HRMS for $C_8H_{18}NO$ $[MH]^+$ calcd, 144.1388; found, 144.1390.

(±)-*trans*-4-Butyl-1-[(9-deazaadenin-9-yl)methyl]-3-hydroxypyrrolidine [(±)-29]. Formaldehyde (95 μL, 1.2 mmol, 37 wt % solution in water) followed by 9-deazaadenine (100 mg, 0.7 mmol) was added to a solution of (±)-**21** (88 mg, 0.66 mmol) in 1,4-dioxane (1.2 mL) and water (2.5 mL). The reaction mixture was stirred at room temperature for 66 h, absorbed onto silica,

and eluted down a silica column using a gradient 10−20% (7 N NH_3 in MeOH) in CH_2Cl_2. The crude product was collected, concentrated, and subjected to flash chromatography (5:4.8:0.2, CH_2Cl_2/MeOH/28% aqueous NH_4OH) to afford (±)-**29** as a pale yellow solid (89 mg, 47%). ^{1}H NMR (500 MHz, CD_3OD): δ = 8.16 (s, 1H), 7.5 (s, 1H), 3.86−3.79 (m, 3H), 3.07 (dd, J = 9.5, 8.0 Hz, 1H), 2.76 (dd, J = 10.4, 6.3 Hz, 1H), 2.71 (dd, J = 10.4, 4.0 Hz, 1H), 2.19 (dd, J = 9.7, 8.0 Hz, 1H), 1.98−1.91 (m, 1H), 1.55−1.48 (m, 1H), 1.35−1.25 (m, 5H), and 0.89 ppm (t, J = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, CD_3OD): δ = 152.1, 151.0, 147.0, 130.1, 115.2, 112.4, 77.7, 62.3, 59.7, 49.0, 48.5, 34.0, 31.5, 23.8, and 14.3 ppm. ESI-HRMS for $C_{15}H_{24}N_5O$ $[MH]^+$ calcd, 290.1981; found, 290.1989.

(±)-Benzyl *trans*-3-Hydroxy-4-isobutylpyrrolidine-1-carboxylate [(±)-14]. A solution of epoxide (***meso*-11**) (203 mg, 0.93 mmol) and CuBr·DMS (30 mg, 0.15 mmol) in THF (8 mL) was cooled to −30 °C. Isobutylmagnesium bromide (2.3 mL, 4.6 mmol, 2 M solution in THF) was added dropwise over 10 min, keeping the internal temperature below −27 °C. After complete addition the mixture was allowed to warm to −15 °C over 80 min and then quenched with 10% aqueous NH_4Cl solution (20 mL) and EtOAc (50 mL). The mixture was stirred at room temperature for 45 min, and then the layers were separated. The aqueous phase was extracted with EtOAc (2 × 50 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford crude (±)-**14** (193 mg, 75%). This material was used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38−7.29 (m, 5H), 5.13 (s, 2H), 4.04−3.98 (m, 1H), 3.74−3.64 (m, 2H), 3.34−3.25 (m, 1H), 3.17−3.09 (m, 1H), 2.17−2.06 (m, 1H), 1.70−1.58 (m, 2H), 1.36−1.25 (m, 1H), 1.20−1.08 (m, 1H), and 0.91 ppm (t, J = 6.6 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.1, 136.9, 128.5, 127.9, 127.9, 75.8, 75.0 (rotamers), 52.9, 52.5 (rotamers), 49.7, 49.5 (rotamers), 44.2, 43.6 (rotamers), 40.7, 26.3, 26.2 (rotamers), 23.2, and 22.1 ppm. ESI-HRMS for $C_{16}H_{23}NO_3Na$ $[MNa]^+$ calcd, 300.1576; found, 300.1575.

(±)-*trans*-3-Hydroxy-4-isobutylpyrrolidine [(±)-22]. Palladium (20 mg, 0.02 mmol, 10 wt % on carbon) was added to a solution of crude (±)-**14** (190 mg, 0.7 mmol) in MeOH (10 mL) under argon. The reaction mixture was placed under a hydrogen atmosphere and stirred for 2 h and then filtered through Celite and concentrated under reduced pressure. Flash chromatography of the residue (gradient 5:4.8:0.2 to 5:4:1, CH_2Cl_2/MeOH/28% aqueous NH_4OH) afforded (±)-**22** as a yellow oil (50 mg, 49%). ^{1}H NMR (500 MHz, CD_3OD): δ = 4.16−4.13 (m, 1H), 3.57 (dd, J = 11.7, 7.3 Hz, 1H), 3.41 (dd, J = 12.3, 5.1 Hz, 1H), 3.16 (dd, J = 12.3, 3.1 Hz, 1H), 3.00 (dd, J = 11.7, 5.8 Hz, 1H), 2.32−2.26 (m, 1H), 1.69−1.61 (m, 1H), 1.39−1.34 (m, 1H), 1.23−1.18 (m, 1H), and 0.95 ppm (dd, J = 10.5, 6.6 Hz, 6H). ^{13}C NMR (125 MHz, CD_3OD): δ = 75.6, 52.5, 50.2, 45.3, 41.4, 27.4, 23.2, and 22.6 ppm. ESI-HRMS for $C_8H_{18}NO$ $[MH]^+$ calcd, 144.1388; found, 144.1382.

(±)-*trans*-1-[(9-Deazaadenin-9-yl)methyl]-3-hydroxy-4-isobutylpyrrolidine [(±)-30]. Formaldehyde (75 μL, 0.9 mmol, 37 wt % solution in water) followed by 9-deazaadenine (52 mg, 0.4 mmol) was added to a solution of (±)-**22** (49 mg, 0.34 mmol) in 1,4-dioxane (0.6 mL) and water (1.2 mL). The reaction mixture was stirred at room temperature for 17 h, absorbed onto silica, and eluted down a silica column with 10% (7 N NH_3 in MeOH) in CH_2Cl_2. The crude product was collected, concentrated, and subjected to flash chromatography (5:4.9:0.1, CH_2Cl_2/MeOH/28% aqueous NH_4OH) to afford (±)-**30** as an off-white solid (42 mg, 42%). ^{1}H NMR (500 MHz, CD_3OD): δ = 8.16 (s, 1H), 7.49 (s, 1H), 3.86−3.78 (m, 3H), 3.09−3.05 (m, 1H), 2.75 (dd, J = 10.4, 6.3 Hz, 1H), 2.70 (dd, J = 10.3, 3.9 Hz, 1H), 2.18−2.14 (m, 1H), 2.09−2.02 (m, 1H), 1.61−1.52 (m, 1H), 1.42−1.36 (m, 1H), 1.23−1.17 (m, 1H), and 0.88 ppm (t, J = 6.7 Hz, 6H). ^{13}C NMR (125 MHz, CD_3OD): δ = 152.1, 150.1, 147.0, 130.1, 115.1, 112.6, 78.1, 62.3, 59.8, 49.1, 46.2, 43.9, 27.7, 23.6, and 22.7 ppm. ESI-HRMS for $C_{15}H_{24}N_5O$ $[MH]^+$ calcd, 290.1981; found, 290.1979.

(±)-Benzyl *trans*-3-Hydroxy-4-(penta-3-yl)pyrrolidine-1-carboxylate [(±)-15]. A solution of epoxide (***meso*-11**) (230 mg, 1.05 mmol) and CuBr·DMS (28 mg, 0.22 mmol) in THF (10 mL) was cooled to −30 °C (internal temperature). 3-Pentylmagnesium bromide (2.3 mL, 4.6 mmol, 2 M solution in ether) was added dropwise over 10 min. After complete addition the mixture was allowed to warm to −20 °C over 30 min and then quenched with 10% aqueous NH_4Cl solution (40 mL) and EtOAc (40 mL). The mixture was stirred at room temperature for 1 h, and then the layers were separated. The aqueous phase was extracted with EtOAc (3 × 40 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Flash chromatography of the residue (2:8, EtOAc/Petrol) afforded (±)-**15** and an unknown corunning minor impurity as a pale yellow oil (195 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37−7.29 (m, 5H), 5.11 (s, 2H), 4.20−4.14 (m, 1H), 3.73−3.69, (m, 1H), 3.67−3.59 (m, 1H), 3.29−3.23 (m, 1H), 3.19−3.14 (m, 1H), 2.14−2.07 (m, 1H), 1.42−1.38 (m, 3H), 1.30−1.20 (m, 2H), and 0.90−0.85 ppm (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.9, 136.9, 128.5, 127.9, 127.8, 73.3, 72.5 (rotamers), 67.4, 66.8 (rotamers), 53.5, 53.1 (rotamers), 48.4, 47.7, 47.4 (rotamers), 41.2, 23.1, 22.4 (rotamers), and 10.9 ppm. ESI-HRMS for $C_{17}H_{25}NO_3Na$ $[MNa]^+$ calcd, 314.1732; found, 314.1731 (for clarity only the data for (±)-**15** are quoted).

(±)-*trans*-3-Hydroxy-4-(penta-3-yl)pyrrolidine [(±)-23]. Palladium (35 mg, 0.03 mmol, 10 wt % on carbon) was added to a solution of crude (±)-**15** (195 mg, 0.9 mmol) in MeOH (10 mL) under argon. The reaction mixture was placed under a hydrogen atmosphere and stirred for 1 h and then filtered through Celite and concentrated under reduced pressure. Flash chromatography of the residue (5:4.9:0.1 then 5:4.8:0.2, CH_2Cl_2/MeOH/28% aqueous NH_4OH) afforded (±)-**23** as a pale yellow gum (27 mg, 16% over two steps). ^{1}H NMR (500 MHz, CD_3OD): δ = 4.07 (m, 1H), 3.15 (dd, J = 11.5, 8.2 Hz, 1H), 2.89 (dd, J = 12.1, 5.8 Hz, 1H), 2.80 (dd, J = 12.1, 3.3 Hz, 1H), 2.50 (dd, J = 11.5, 8.5 Hz, 1H), 1.94 (q, J = 8.2, 4.4 Hz, 1H), 1.54−1.39 (m, 3H), 1.32−1.21 (m, 2H), and 0.91 ppm (dt, J = 12.9, 7.4 Hz, 6H). ^{13}C NMR (125 MHz, CD_3OD): δ = 76.7, 56.0, 52.1, 50.5, 43.4, 24.4, 23.6, 11.4, and 11.0 ppm. ESI-HRMS for $C_9H_{20}NO$ $[MH]^+$ calcd, 158.1545; found, 158.1540.

(±)-*trans*-1-[(9-Deazaadenin-9-yl)methyl]-3-hydroxy-4-(penta-3-yl)pyrrolidine [(±)-31]. Formaldehyde (25 μL, 0.3 mmol, 37 wt % solution in water) followed by 9-deazaadenine (30 mg, 0.22 mmol) was added to a solution of (±)-**23** (27 mg, 0.17 mmol) in 1,4-dioxane (0.6 mL) and water (0.6 mL). The reaction mixture was stirred at room temperature for 17 h, absorbed onto silica, and eluted down a silica column with a gradient of 5−20% (7 N NH_3 in MeOH) in CH_2Cl_2. The crude product was collected, concentrated, and subjected to flash chromatography (5:4.9:0.1, CH_2Cl_2/MeOH/28% aqueous NH_4OH) to afford (±)-**31** as a pale yellow solid (24 mg, 33%). ^{1}H NMR (500 MHz, CD_3OD): δ = 8.16 (s, 1H), 7.50 (s, 1H), 3.99−3.96 (m, 1H), 3.84 (d, J = 13.4 Hz, 1H), 3.77 (d, J = 13.4 Hz, 1H), 3.04 (t, J = 8.8 Hz, 1H), 2.79 (dd, J = 10.4, 2.3 Hz, 1H), 2.62 (dd, J = 10.4, 6.4 Hz, 1H), 2.17 (t, J = 9.5 Hz, 1H), 2.04−1.98 (m, 1H), 1.51−1.37 (m, 3H), 1.27−1.19 (m, 2H), 0.89 (t, J = 7.4, 3H), and 0.84 ppm (t, J = 7.1, 3H). ^{13}C NMR (125 MHz, CD_3OD): δ = 152.1, 151.0, 147.0, 130.1, 115.2, 112.5, 75.8, 63.3, 58.2, 51.3, 49.1, 44.3, 24.0, 23.6, 11.3, and 10.7 ppm. ESI-HRMS for $C_{16}H_{26}N_5O$ $[MH]^+$ calcd, 304.2137; found, 304.2137.

(±)-Benzyl *trans*-4-Cyclopropyl-3-hydroxypyrrolidine-1-carboxylate [(±)-16]. A solution of epoxide (***meso*-11**) (283 mg, 1.3 mmol) and CuBr·DMS (43 mg, 0.21 mmol) in THF (10 mL) was cooled to −30 °C (internal temperature). Cyclopropylmagnesium bromide (10 mL, 5.0 mmol, 0.5 M solution in THF) was added dropwise over 25 min. After complete addition the mixture was allowed to slowly warm to −15 °C over 45 min and then quenched with 10% aqueous NH_4Cl solution (20 mL) and EtOAc (50 mL). The mixture was stirred at room temperature for 40 min, and then the layers were separated. The aqueous

phase was extracted with EtOAc (3 × 50 mL), and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Flash chromatography of the residue (3:7 then 4:6, EtOAc/Petrol) afforded (±)-**16** as a pale yellow oil (311 mg, 92%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38−7.29 (m, 5H), 5.13 (s, 2H), 4.25−4.22 (m, 1H), 3.75−3.70 (m, 1H), 3.69−3.63 (m, 1H), 3.40−3.28 (m, 1H), 1.94−1.85 (m, 1H), 1.48−1.43 (m, 1H), 0.60−0.44 (m, 3H), 0.30−0.25 (m, 1H), and 0.16−0.10 ppm (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.1, 136.9, 128.5, 128.0, 127.9, 75.8, 75.0 (rotamers), 66.9, 53.3, 52.8 (rotamers), 51.3, 50.5 (rotamers), 49.2, 49.1 (rotamers), 12.4, 12.2 (rotamers), 3.4, 3.4 (rotamers), 3.1 and 3.0 (rotamers) ppm. ESI-HRMS for $C_{15}H_{19}NO_3Na$ $[MNa]^+$ calcd, 284.1263; found, 284.1260.

(±)-***trans*-4-Cyclopropyl-3-hydroxypyrrolidine [(±)-24].** Palladium (25 mg, 0.02 mmol, 10 wt % on carbon) was added to a solution of (±)-**16** (310 mg, 1.2 mmol) in MeOH (20 mL) under argon. The reaction mixture was placed under a hydrogen atmosphere and stirred for 1 h and then filtered through Celite and concentrated under reduced pressure. Flash chromatography of the residue (5:4.6:0.4, CH_2Cl_2/MeOH/28% aqueous NH_4OH) afforded (±)-**24** as an off-white solid (126 mg, 84%). ^{1}H NMR (500 MHz, CD_3OD): δ = 4.30 (dt, J = 5.0, 2.7 Hz, 1H), 3.51 (dd, J = 11.7, 7.3 Hz, 1H), 3.43 (dd, J = 12.4, 4.7 Hz, 1H), 3.17 (dd, J = 12.3, 2.2 Hz, 1H), 3.11 (dd, J = 11.7, 4.6 Hz, 1H), 1.61−1.55 (m, 1H), 0.71−0.63 (m, 1H), 0.57−0.48 (m, 1H), 0.33−0.29 (m, 1H), and 0.21−0.17 ppm (m, 1H). ^{13}C NMR (125 MHz, CD_3OD): δ = 76.4, 52.9, 52.6, 50.0, 13.2, 4.2, and 3.6 ppm. ESI-HRMS for $C_7H_{14}NO$ $[MH]^+$ calcd, 128.1075; found, 128.1082.

(±)-***trans*-4-Cyclopropyl-1-[(9-deazaadenin-9-yl)methyl]-3-hydroxypyrrolidine [(±)-32].** Formaldehyde (50 μL, 0.6 mmol, 37 wt % solution in water) followed by 9-deazaadenine (60 mg, 0.45 mmol) was added to a solution of (±)-**24** (51 mg, 0.40 mmol) in 1,4-dioxane (1 mL) and water (1 mL). The reaction mixture was stirred at room temperature for 41 h, absorbed onto silica, and eluted down a silica column with a gradient of 5−30% (7 N NH_3 in MeOH) in CH_2Cl_2. The crude product was collected, concentrated, and subjected to flash chromatography (5:4.5:0.5, CH_2Cl_2/MeOH/28% aqueous NH_4OH) to afford (±)-**32** as an off-white solid (59 mg, 54%). ^{1}H NMR (500 MHz, CD_3OD): δ = 8.16 (s, 1H), 7.45 (s, 1H), 4.05 (dt, J = 6.4, 4.1 Hz, 1H), 3.85 (d, J = 13.4 Hz, 1H), 3.80 (d, J = 13.4 Hz, 1H), 3.02 (dd, J = 9.6, 8.1 Hz, 1H), 2.82 (dd, J = 10.5, 6.4 Hz, 1H), 2.68 (dd, J = 10.4, 3.9 Hz, 1H), 2.36 (dd, J = 9.8, 7.5 Hz, 1H), 1.38 (ddd, J = 16.9, 7.8, 4.3 Hz, 1H), 0.75−0.68 (m, 1H), 0.46−0.37 (m, 2H), 0.28−0.24 (m, 1H), and 0.08−0.03 ppm (m, 1H). ^{13}C NMR (125 MHz, CD_3OD): δ = 152.1, 151.0, 147.0, 130.1, 115.2, 112.5, 77.4, 62.6, 59.1, 53.6, 49.1, 14.5, 3.8, and 3.5 ppm. ESI-HRMS for $C_{14}H_{20}N_5O$ $[MH]^+$ calcd, 274.1668; found, 274.1666.

(±)-**Benzyl *trans*-4-Cyclopentyl-3-hydroxypyrrolidine-1-carboxylate [(±)-17].** Cyclopentyl bromide (0.5 mL, 4.7 mmol) was added dropwise to a suspension of magnesium (221 mg, 9 mmol) in THF (10 mL), activated with 1,2-dibromoethane. After complete addition the reaction mixture was stirred for 1 h at room temperature and then added dropwise, over 10 min, to a solution of epoxide (***meso*-11**) (230 mg, 1 mmol) and CuBr·DMS (55 mg, 0.3 mmol) in THF (10 mL) at −30 °C (internal temperature). The reaction mixture was stirred for 75 min and then quenched with 10% aqueous NH_4Cl solution (20 mL) and EtOAc (20 mL). The biphasic mixture was stirred for 1 h and then the layers were separated, and the aqueous phase was extracted with EtOAc (2 × 50 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford the crude (±)-**17** as a pale yellow oil, which was used immediately in the next step without characterization.

(±)-***trans*-4-Cyclopentyl-3-hydroxypyrrolidine [(±)-25].** Palladium (50 mg, 0.05 mmol, 10 wt % on carbon) was added to a solution of crude (±)-**17** in MeOH (20 mL) under argon. The reaction mixture was placed under a hydrogen atmosphere and stirred for 1 h, and then further catalyst (50 mg) was added. The reaction mixture was placed under a hydrogen atmosphere for a further 1 h and then filtered through Celite and concentrated under reduced pressure. Flash chromatography of the residue (5:4.6:0.4, CH_2Cl_2/MeOH/28% aqueous NH_4OH) afforded crude (±)-**25** (43 mg) which was used without further purification and characterization in the next step.

(±)-***trans*-4-Cyclopentyl-1-[(9-deazaadenin-9-yl)methyl]-3-hydroxypyrrolidine [(±)-33].** Formaldehyde (35 μL, 0.4 mmol, 37 wt % solution in water) followed by 9-deazaadenine (42 mg, 0.3 mmol) was added to a solution of crude (±)-**25** (43 mg) in 1,4-dioxane (1 mL) and water (1 mL). The reaction mixture was stirred at room temperature for 94 h, absorbed onto silica, and eluted down a silica column with a gradient of 5−30% (7 N NH_3 in MeOH) in CH_2Cl_2. The crude product was collected, concentrated, and subjected to flash chromatography (5:4.95:0.05, CH_2Cl_2/MeOH/28% aqueous NH_4OH) to afford (±)-**33** as an off-white solid (28 mg, 10%, over three steps). ^{1}H NMR (500 MHz, CD_3OD): δ = 8.16 (s, 1H), 7.50 (s, 1H), 3.97−3.94 (m, 1H), 3.85 (d, J = 13.4 Hz, 1H), 3.80 (d, J = 13.4 Hz, 1H), 3.06 (dd, J = 9.6, 8.1 Hz, 1H), 2.76−2.68 (m, 2H), 2.39 (dd, J = 9.7, 8.1 Hz, 1H), 1.89−1.50 (m, 8H), 1.34−1.30 (m, 1H) and 1.21−1.08 ppm (m, 1H). ^{13}C NMR (125 MHz, CD_3OD): δ = 152.1, 151.0, 147.0, 130.2, 115.2, 112.4, 76.7, 63.0, 59.1, 54.2, 49.1, 44.7, 32.2, 31.8, and 26.1 (2C) ppm. ESI-HRMS for $C_{16}H_{23}N_5ONa$ $[MNa]^+$ calcd, 324.1800; found, 324.1802.

(±)-**Benzyl *trans*-4-(Cyclohexylmethyl)-3-hydroxypyrrolidine-1-carboxylate [(±)-18].** A solution of epoxide (***meso*-11**) (243 mg, 1.1 mmol) and CuBr·DMS (50 mg, 0.22 mmol) in THF (10 mL) was cooled to −30 °C (internal temperature). Cyclohexylmethylmagnesium bromide (11 mL, 5.5 mmol, 0.5 M solution in THF) was added dropwise over 20 min. After complete addition the mixture was allowed to warm to −25 °C over 30 min and then quenched with 10% aqueous NH_4Cl solution (20 mL) and EtOAc (20 mL). The mixture was stirred at room temperature for 30 min, and then the layers were separated. The aqueous phase was extracted with EtOAc (3 × 30 mL), and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Flash chromatography of the residue (gradient 2:8 to 4:6, EtOAc/Petrol) afforded (±)-**18** as an off-white solid (286 mg, 81%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.40−7.30 (m, 5H), 5.13 (s, 2H), 4.01 (t, J = 4.8 Hz, 1H), 3.72−3.64 (m, 2H), 3.33−3.26 (m, 1H), 3.16−3.10 (m, 1H), 2.19−2.11 (m, 1H), 1.74−1.64 (m, 6H), 1.36−1.07 (m, 6H), and 0.95−0.81 ppm (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.1, 137.0, 128.5, 128.0, 127.9, 75.9, 75.1 (rotamers), 66.8, 52.9, 52.5 (rotamers), 49.8, 49.5 (rotamers), 43.5, 43.0 (rotamers), 39.4, 39.2 (rotamers), 35.8, 35.7 (rotamers), 34.0, 32.9, 26.5, 26.2, and 26.2 ppm. ESI-HRMS for $C_{19}H_{27}NO_3Na$ $[MNa]^+$ calcd, 340.1895; found, 340.1895.

(±)-***trans*-4-(Cyclohexylmethyl)-3-hydroxypyrrolidine [(±)-26].** Palladium (20 mg, 0.02 mmol, 10 wt % on carbon) was added to a solution of (±)-**18** (286 mg, 0.9 mmol) in MeOH (10 mL) under argon. The reaction mixture was placed under a hydrogen atmosphere and stirred for 1 h, and then further catalyst (20 mg, 0.02 mmol, 10 wt % on carbon) was added. The reaction mixture was stirred under a hydrogen atmosphere for a further 1 h and then filtered through Celite and concentrated under reduced pressure. Flash chromatography of the residue (5:4.8:0.2 and then 5:4.5:0.5, CH_2Cl_2/MeOH/28% aqueous NH_4OH) afforded (±)-**26** as an off-white solid (115 mg, 70%). ^{1}H NMR (500 MHz, CD_3OD): δ = 3.88 (q, J = 4.2 Hz, 1H), 3.20 (dd, J = 11.2, 7.6 Hz, 1H), 2.97 (dd, J = 12.0, 5.5 Hz, 1H), 2.76 (dd, J = 12.0, 3.4 Hz, 1H), 2.45 (dd, J = 11.2, 6.4 Hz, 1H), 2.07−2.01 (m, 1H), 1.80−1.65 (m, 5H), 1.39−1.10 (m, 6H), and 0.97−0.86 ppm (m, 2H). ^{13}C NMR (125 MHz, CD_3OD): δ = 78.8, 54.5, 52.1, 46.2, 41.6, 37.4, 35.1, 34.3, 27.7, and 27.4 (2 × C) ppm. ESI-HRMS for $C_{11}H_{22}NO$ $[MH]^+$ calcd, 184.1701; found, 184.1696.

(±)-***trans*-4-(Cyclohexylmethyl)-1-[(9-deaza-adenin-9-yl)methyl]-3-hydroxypyrrolidine [(±)-34].** Formaldehyde (35 μL, 0.4 mmol, 37 wt % solution in water) followed by 9-deazaadenine (42 mg,

0.31 mmol) was added to a solution of (±)-**26** (51 mg, 0.28 mmol) in 1,4-dioxane (1.5 mL) and water (1.5 mL). The reaction mixture was stirred at room temperature for 67 h, absorbed onto silica, and eluted down a silica column with a gradient of 5−30% (7 N NH_3 in MeOH) in CH_2Cl_2. The crude product was collected, concentrated, and subjected to flash chromatography (5:4.9:0.1, CH_2Cl_2/MeOH/28% aqueous NH_4OH) to afford (±)-**34** as a pale yellow solid (42 mg, 46%). ^{1}H NMR (500 MHz, CD_3OD): δ = 8.16 (s, 1H), 7.49 (s, 1H), 3.86−3.78 (m, 3H), 3.08−3.05 (m, 1H), 2.75 (dd, J = 10.4, 6.4 Hz, 1H), 2.70 (dd, J = 10.4, 4.0 Hz, 1H), 2.16 (dd, J = 9.5, 8.1 Hz, 1H), 2.11−2.01 (m, 1H), 1.75−1.62 (m, 5H), 1.43−1.38 (m, 1H), 1.28−1.11 (m, 5H), and 0.95−0.81 ppm (m, 2H). ^{13}C NMR (125 MHz, CD_3OD): δ = 152.1, 151.1, 147.0, 130.1, 115.1, 112.5, 78.1, 62.2, 59.8, 49.1, 45.8, 42.4, 37.4, 35.1, 34.2, 27.7, and 27.4 (2 × C) ppm. ESI-HRMS for $C_{18}H_{28}N_5O$ $[MH]^+$ calcd, 330.2294; found, 330.2297.

(±)-**Benzyl *trans*-3-Hydroxy-4-phenylpyrrolidine-1-carboxylate [(±)-19].** A solution of epoxide (***meso*-11**) (149 mg, 0.68 mmol) and CuBr·DMS (30 mg, 0.15 mmol) in THF (5.6 mL) was cooled to −30 °C. Phenylmagnesium bromide (1.5 mL, 1.5 mmol, 1 M solution in THF) was added dropwise over 10 min, keeping the internal temperature below −25 °C. After complete addition the mixture was allowed to warm to −15 °C over 90 min and then cooled back to −30 °C, and further phenylmagnesium bromide (1.5 mL, 1.5 mmol, 1 M solution in THF) was added. The reaction mixture was allowed to warm to −20 °C over 1 h and then quenched with 10% aqueous NH_4Cl solution (20 mL) and EtOAc (20 mL). The mixture was stirred at room temperature for 30 min, and then the layers were separated. The aqueous phase was extracted with EtOAc (3 × 20 mL), and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Flash chromatography of the residue (gradient 3:7 to 1:1, EtOAc/Petrol) afforded a mixture of (±)-**19** and unreacted epoxide (***meso*-11**) as a pale yellow oil (162 mg, 2:1, (±)-**19**/***meso*-11**) which was used without characterization.

(±)-***trans*-3-Hydroxy-4-phenylpyrrolidine [(±)-27].** Palladium (25 mg, 0.02 mmol, 10 wt % on carbon) was added to a solution of (±)-**19**/***meso*-11** (2: 1) (160 mg) in MeOH (12 mL) under argon. The reaction mixture was placed under a hydrogen atmosphere and stirred for 75 min and then filtered through Celite and concentrated under reduced pressure. Flash chromatography of the residue (5:4.8:0.2 then 5:4.6:0.4, CH_2Cl_2/MeOH/28% aqueous NH_4OH) afforded (±)-**27** as a yellow oil (39 mg, 35%, over two steps). ^{1}H NMR (500 MHz, CD_3OD): δ = 7.32−7.26 (m, 4H), 7.22−7.19 (m, 1H), 4.30−4.27 (m, 1H), 3.46 (dd, J = 11.5, 8.2 Hz, 1H), 3.18 (dd, J = 11.9, 6.0 Hz, 1H), 3.12 (td, J = 8.2, 5.4 Hz, 1H), and 2.92−2.88 ppm (m, 2H). ^{13}C NMR (125 MHz, CD_3OD): δ = 142.7, 129.7, 128.5, 127.8, 80.0, 55.3, 54.9, and 53.6 ppm. ESI-HRMS for $C_{10}H_{14}NO$ $[MH]^+$ calcd 164.1075; found, 164.1068.

(±)-***trans*-1-[(9-Deazaadenin-9-yl)methyl]-3-hydroxy-4-phenylpyrrolidine [(±)-35].** Formaldehyde (35 μL, 0.4 mmol, 37 wt % solution in water) followed by 9-deazaadenine (39 mg, 0.24 mmol) was added to a solution of (±)-**27** (30 mg, 0.22 mmol) in 1,4-dioxane (0.4 mL) and water (0.8 mL). The reaction mixture was stirred at room temperature for 17 h, absorbed onto silica, and eluted down a silica column with a gradient of 10−20% (7 N NH_3 in MeOH) in CH_2Cl_2. The crude product was collected, concentrated, and subjected to flash chromatography (5:4.9:0.1 then 5:4.8:0.2, CH_2Cl_2/MeOH/28% aqueous NH_4OH) to afford (±)-**35** as a white solid (38 mg, 55%). ^{1}H NMR (500 MHz, CD_3OD): δ = 8.17 (s, 1H), 7.52 (s, 1H), 7.26 (br s, 2H), 7.25 (br s, 2H), 7.18−7.15 (m, 1H), 4.28−4.25 (m, 1H), 3.89 (q, J = 13.4 Hz, 2H), 3.28−3.25 (m, 1H), 3.16 (td, J = 8.7, 5.7 Hz, 1H), 3.00 (dd, J = 10.3, 6.8 Hz, 1H), 2.85 (dd, J = 10.3, 4.3 Hz, 1H), and 2.64 ppm (t, J = 9.3 Hz, 1H). ^{13}C NMR (125 MHz, CD_3OD): δ = 152.1, 151.0, 147.0, 143.6, 130.1, 129.5, 128.6, 127.5, 115.2, 112.6, 79.3, 62.8, 61.2, 54.9, and 49.1 ppm. ESI-HRMS for $C_{17}H_{19}N_5O$-Na $[MNa]^+$ calcd, 332.1487; found, 332.1490.

(±)-***tert*-Butyl *trans*-3-Hydroxy-4-vinylpyrrolidine-1-carboxylate [(±)-36].**[23] A solution of epoxide (***meso*-10**) (331 mg, 1.8 mmol) and CuBr·DMS (73 mg, 0.35 mmol) in THF (15 mL) was cooled to −30 °C (internal temperature). Vinylmagnesium bromide (8 mL, 8.0 mmol, 1 M solution in THF) was added dropwise over 15 min. After complete addition the reaction was allowed to slowly warm to −10 °C over 1 h and then quenched with 10% aqueous NH_4Cl solution (20 mL) and EtOAc (50 mL). The mixture was stirred at room temperature for 1 h, and then the layers were separated. The aqueous phase was extracted with EtOAc (3 × 50 mL), and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford (±)-**36** as a pale yellow oil (286 mg, 75%). No further purification was necessary. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.74−5.67 (m, 1H), 5.20 (d, J = 17.2 Hz, 1H), 5.15 (d, J = 10.4 Hz, 1H), 4.14−4.08 (m, 1H), 3.73−3.61 (m, 2H), 3.29−3.17 (m, 2H), 2.71−2.65 (m, 1H), 2.71 (br s, 1H), and 1.46 ppm (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.5, 136.3, 117.3, 79.5, 74.5, 74.2 (rotamers), 52.2, 51.9 (rotamers), 50.5, 49.9 (rotamers), 48.8, 48.3 (rotamers), and 28.5 ppm. ESI-HRMS for $C_{11}H_{19}NO_3Na$ $[MNa]^+$ calcd, 236.1263; found, 236.1263.

(±)-***trans*-3-Hydroxy-4-vinylpyrrolidine [(±)-38].**[23] Aqueous HCl (36%, 1 mL) was added to a solution of (±)-**36** (286 mg, 1.34 mmol) in MeOH (20 mL). The reaction mixture was concentrated under reduced pressure and then azeotroped with MeOH (20 mL) followed by toluene (20 mL). Flash chromatography of the residue (5:4.6:0.4, CH_2Cl_2/MeOH/28% aqueous NH_4OH) afforded (±)-**38** as a brown oil (95 mg, 63%). ^{1}H NMR (500 MHz, CD_3OD): δ = 5.78 (ddd, J = 17.3, 10.4, 7.9 Hz, 1H), 5.12 (dt, J = 17.3, 1.5 Hz, 1H), 5.06 (ddd, J = 10.4, 1.5, 1.0 Hz, 1H), 4.03 (dt, J = 5.6, 4.3 Hz, 1H), 3.21 (dd, J = 11.4, 7.6 Hz, 1H), 3.03 (dd, J = 11.9, 5.7 Hz, 1H), 2.77 (dd, J = 11.8, 4.1 Hz, 1H), 2.68 (dd, J = 11.3, 6.7 Hz, 1H), and 2.61−2.56 ppm (m, 1H). ^{13}C NMR (125 MHz, CD_3OD): δ = 139.4, 116.1, 78.3, 54.6, 53.5, and 51.3 ppm. ESI-HRMS for $C_6H_{12}NO$ $[MH]^+$ calcd, 144.0919; found, 114.0911.

(±)-***trans*-1-[(9-Deazaadenin-9-yl)methyl]-3-hydroxy-4-vinylpyrrolidine [(±)-40].** Formaldehyde (45 μL, 0.56 mmol, 37 wt % solution in water) followed by 9-deazaadenine (61 mg, 0.46 mmol) was added to a solution of (±)-**38** (42 mg, 0.37 mmol) in 1,4-dioxane (1 mL) and water (1 mL). The reaction mixture was stirred at room temperature for 17 h, absorbed onto silica, and eluted down a silica column with a gradient of 5−20% (7 N NH_3 in MeOH) in CH_2Cl_2. The crude product was collected, concentrated, and subjected to flash chromatography (5:4.5:0.5, CH_2Cl_2/MeOH/28% aqueous NH_4OH) to afford (±)-**40** as an off-white solid (55 mg, 57%). ^{1}H NMR (500 MHz, CD_3OD): δ = 8.16 (s, 1H), 7.49 (s, 1H), 5.79 (ddd, J = 17.2, 10.3, 8.0 Hz, 1H), 5.06 (dt, J = 17.2, 1.4 Hz, 1H), 4.99 (dq, J = 10.3, 1.0 Hz, 1H), 4.01−3.98 (m, 1H), 3.87 (d, J = 13.5 Hz, 1H), 3.82 (d, J = 13.5 Hz, 1H), 3.05 (dd, J = 9.8, 8.1 Hz, 1H), 2.86 (dd, J = 10.4, 6.7 Hz, 1H), 2.73 (dd, J = 10.4, 4.5 Hz, 1H), 2.65−2.59 (m, 1H), and 2.42 ppm (dd, J = 9.9, 8.3 Hz, 1H). ^{13}C NMR (125 MHz, CD_3OD): δ = 152.1, 151.0, 147.0, 139.7, 130.3, 116.0, 115.2, 112.1, 77.2, 61.9, 58.7, 52.9, and 49.1 ppm. ESI-HRMS for $C_{13}H_{18}N_5O$ $[MH]^+$ calcd, 260.1511; found, 260.1511.

(±)-***tert*-Butyl *trans*-4-Allyl-3-hydroxypyrrolidine-1-carboxylate [(±)-37].**[23] A solution of epoxide (***meso*-10**) (227 mg, 1.2 mmol) in diethyl ether (2.6 mL) was added dropwise to a solution of allylmagnesium chloride (1.4 mL, 2.8 mmol, 2 M solution in THF) in diethyl ether (4.4 mL) at 0 °C (internal temperature). The reaction mixture was stirred at 0 °C for 15 min and then warmed to room temperature. After 90 min the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl solution (20 mL) and then extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with brine (2 × 50 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Flash chromatography of the residue (1:9, EtOAc/Petrol) afforded (±)-**37** as a pale yellow oil (138 mg, 50%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.82−5.75

(m, 1H), 5.09−5.04 (m, 2H), 4.04 (dd, J = 10.1, 4.8 Hz, 1H), 3.64−3.54 (m, 2H), 3.26−3.21 (m, 1H), 3.11−3.05 (m, 1H), 2.24−2.19 (m, 1H), 2.17−2.11 (m, 1H), 2.07−1.98 (m, 1H), and 1.45 ppm (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.8, 135.8, 116.7, 79.5, 74.7, 74.0 (rotamers), 52.7, 52.4 (rotamers), 49.0, 48.7 (rotamers), 45.5, 45.0 (rotamers), 35.6, and 28.7 ppm. ESI-HRMS for $C_{12}H_{21}NO_3Na$ $[MNa]^+$ calcd, 250.1419; found, 250.1416.

(±)-*trans*-4-Allyl-3-hydroxypyrrolidine [(±)-39].[23] Aqueous HCl (36%, 1 mL, 33 mmol) was added to a stirred solution of **(±)-37** (59 mg, 0.26 mmol) in methanol (5 mL). The reaction mixture was concentrated under reduced pressure and subsequently azeotroped with methanol (10 mL) followed by toluene (10 mL). The residue was absorbed onto silica and eluted down a flash column (5:4.5:0.5, CH_2Cl_2/MeOH/28% aqueous NH_4OH) to afford **(±)-39** as a yellow oil (40 mg, 95%). ^{1}H NMR (500 MHz, CD_3OD): δ = 5.87−5.79 (m, 1H), 5.08−5.00 (m, 2H), 3.95−3.93 (m, 1H), 3.15 (dd, J = 11.5, 7.0 Hz, 1H), 2.95 (dd, J = 12.0, 5.5 Hz, 1H), 2.74 (dd, J = 12.0, 3.4 Hz, 1H), 2.48 (dd, J = 11.6, 5.5 Hz, 1H), 2.24−2.19 (m, 1H), and 2.04−1.96 ppm (m, 2H). ^{13}C NMR (125 MHz, CD_3OD): δ = 136.7, 116.7, 77.4, 54.3, 51.0, 48.3, and 37.3 ppm. ESI-HRMS for $C_7H_{14}NO$ $[MH]^+$ calcd, 128.1075; found, 128.1072.

(±)-*trans*-4-Allyl-1-[(9-deazaadenin-9-yl)methyl]-3-hydroxypyrrolidine [(±)-41]. Formaldehyde (44 μL, 0.54 mmol, 37 wt % solution in water) followed by 9-deazaadenine (44 mg, 0.33 mmol) was added to a solution of **(±)-39** (40 mg, 0.32 mmol) in 1,4-dioxane (0.6 mL) and water (1.2 mL). The reaction mixture was stirred at room temperature for 17 h, absorbed onto silica, and eluted down a silica column with a gradient of 5−40% (7 N NH_3 in MeOH) in CH_2Cl_2. The crude product was collected, concentrated, and subjected to flash chromatography (5:4.9:0.1, CH_2Cl_2/MeOH/28% aqueous NH_4OH) to afford **(±)-41** as an off-white solid (20 mg, 24%). ^{1}H NMR (500 MHz, CD_3OD): δ = 8.16 (s, 1H), 7.49 (s, 1H), 5.83−5.74 (m, 1H), 5.05−4.95 (m, 2H), 3.89 (dt, J = 6.3, 4.1 Hz, 1H), 3.85 (d, J = 13.4 Hz, 1H), 3.80 (d, J = 13.6 Hz, 1H), 3.02 (dd, J = 9.9, 7.6 Hz, 1H), 2.80 (dd, J = 10.4, 6.4 Hz, 1H), 2.68 (dd, J = 10.4, 4.1 Hz, 1H), 2.30−2.24 (m, 2H), and 2.10−2.02 ppm (m, 2H). ^{13}C NMR (125 MHz, CD_3OD): δ = 152.1, 151.0, 147.0, 138.0, 130.1, 116.3, 115.1, 112.5, 76.8, 62.2, 59.0, 49.1, 48.0, and 38.2 ppm. ESI-HRMS for $C_{14}H_{20}N_5O$ $[MH]^+$ calcd, 274.1668; found, 274.1661.

(±)-*tert*-Butyl *trans*-3-Hydroxy-4-((trimethylsilyl)ethynyl)-pyrrolidine-1-carboxylate [(±)-42]. *n*-Butyllithium (4.6 mL, 6.0 mmol, 1.3 M solution in hexanes) was added, over 5 min, to a solution of trimethylsilylacetylene (1.1 mL, 7.8 mmol) in THF (8.5 mL) at −78 °C. After 30 min $BF_3 \cdot OEt_2$ (1.4 mL, 11.4 mmol) was added over 5 min. After the mixture was stirred for a further 30 min at −78 °C, a solution of epoxide (***meso*-10**) (550 mg, 3.0 mmol) in THF (10 mL) was added. The reaction mixture was stirred at −78 °C for 1.5 h and then allowed to warm to room temperature. The mixture was stirred for 16 h and then quenched by the addition of saturated aqueous NH_4Cl solution (20 mL) and then partitioned between water (50 mL) and EtOAc (50 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with brine (2 × 50 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Flash chromatography of the residue (2:8, EtOAc/Petrol) afforded **(±)-42** as a yellow gum (478 mg, 57%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.33 (q, J = 4.7, 1H), 3.77−3.65 (br m, 2H), 3.48−3.36 (br m, 1H), 3.32−3.22 (br m, 1H), 2.90 (br s, 1H), 1.58 (br s, 1H), 1.46 (s, 9H), and 0.15 ppm (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.7, 104.7, 87.8, 79.8, 75.5, 74.7 (rotamers), 52.4, 52.1 (rotamers), 49.9, 49.4 (rotamers), 39.2, 38.7 (rotamers), 28.5, and 0.0 ppm. ESI-HRMS for $C_{14}H_{25}NO_3NaSi$ $[MNa]^+$ calcd, 306.1501; found, 306.1505.

(±)-*trans*-3-Hydroxy-4-((trimethylsilyl)ethynyl)pyrrolidine [(±)-43]. Aqueous HCl (36%, 1 mL, 33 mmol) was added to a solution of **(±)-42** (478 mg, 1.7 mmol) in methanol (20 mL) and then concentrated under reduced pressure. The residue was subsequently azeotroped with methanol (20 mL) followed by toluene (20 mL) and then absorbed on to silica and eluted down a flash column (5:4.8:0.2, CH_2Cl_2/MeOH/28% aqueous NH_4OH) to afford **(±)-43** as a yellow solid (276 mg, 89%). ^{1}H NMR (500 MHz, CD_3OD): δ = 4.28 (dt, J = 5.0, 2.8 Hz, 1H), 3.35 (dd, J = 11.2, 7.4 Hz, 1H), 3.09 (dd, J = 12.2, 5.0 Hz, 1H), 2.87−2.78 (m, 3H), and 0.13 ppm (s, 9H). ^{13}C NMR (125 MHz, CD_3OD): δ = 107.6, 87.6, 79.0, 54.8, 52.8, 41.8, and 0.0 ppm. ESI-HRMS for $C_9H_{18}NOSi$ $[MH]^+$ calcd, 184.1158; found, 184.1161.

(±)-*trans*-1-[(9-Deazaadenin-9-yl)methyl]-3-hydroxy-4-((trimethylsilyl)ethynyl)pyrrolidine [(±)-44]. Formaldehyde (55 μL, 0.69 mmol, 37 wt % solution in water) followed by 9-deazaadenine (73 mg, 0.54 mmol) was added to a solution of **45** (81 mg, 0.44 mmol) in 1,4-dioxane (2.5 mL) and water (2.5 mL). The reaction mixture was stirred at room temperature for 66 h and then concentrated under reduced pressure. Crude **(±)-44** was used directly in the next step without characterization.

(±)-*trans*-1-[(9-Deazaadenin-9-yl)methyl]-4-ethynyl-3-hydroxypyrrolidine [(±)-45]. Sodium methoxide (10 μL, 0.05 mmol, 30 wt % solution in methanol) was added to a solution of crude **(±)-44** (145 mg, 0.44 mmol) in methanol (5 mL). The reaction mixture was stirred at room temperature for 2.5 h, and then further sodium methoxide (10 μL, 0.05 mmol, 30 wt % solution in methanol) was added. After being stirred for a further 17 h, the reaction mixture was absorbed onto silica and eluted down a silica column (5:4.95:0.05, CH_2Cl_2/MeOH/28% aqueous NH_4OH) to afford **(±)-45** (29 mg, 25%). A sample was purified by preparative HPLC to analytical purity as a TFA salt. ^{1}H NMR (500 MHz, CD_3OD): δ = 8.47 (s, 1H), 8.07 (s, 1H), 4.68 (s, 2H), 4.53 (quin, J = 2.2 Hz. 1H), 3.91 (dd, J = 11.8, 7.4 Hz, 1H), 3.74 (dd, J = 12.3, 4.1 Hz, 1H), 3.59 (dd, J = 11.7, 4.1 Hz, 1H), 3.49 (d, J = 12.4 Hz, 1H), 3.22−3.19 (m, 1H), and 2.78 ppm (d, J = 2.6 Hz, 1H). ^{13}C NMR (125 MHz, CD_3OD): δ = 159.2, 152.2, 145.3, 136.0, 114.1, 104.3, 81.2, 75.9, 75.1, 60.5, 58.1, 50.2, and 39.2 ppm (resonance signals due to CF_3COOH have not been quoted). ESI-HRMS for $C_{13}H_{16}N_5O$ $[MH]^+$ calcd, 258.1355; found, 258.1355.

(±)-*tert*-Butyl *trans*-4-Azido-3-hydroxypyrrolidine-1-carboxylate [(±)-46].[29] Sodium azide (1.02 g, 15.7 mmol) was added to a solution of epoxide (***meso*-10**) (1.0 g, 5.4 mmol) in 1,4-dioxane (9 mL) and water (1.8 mL). The resulting suspension was heated to 100 °C for 65 h and then cooled to 0 °C, and water (20 mL) was added. The mixture was extracted with EtOAc (3 × 50 mL), and the combined organic phases were washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Flash chromatography of the residue (3:7, then 4:6, EtOAc/Petrol) afforded **(±)-46** as a pale yellow oil (1.21 g, 98%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.23 (br s, 1H), 3.93 (br s, 1H), 3.70−3.66 (m, 1H), 3.60−3.56 (m, 1H), 3.46−3.16 (m, 3H), and 1.46 ppm (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.6, 80.3, 74.1, 73.3 (rotamers), 65.4, 64.9 (rotamers), 51.9, 51.6 (rotamers), 48.7, 48.2 (rotamers), and 28.4 ppm. ESI-HRMS for $C_9H_{16}N_4O_3Na$ $[MNa]^+$ calcd, 251.1120; found, 251.1121.

(±)-*tert*-Butyl *trans*-3-Hydroxy-4-(5-(trimethylsilyl)-1*H*-1,2,3-triazol-1-yl)pyrrolidine-1-carboxylate [(±)-47]. Trimethylsilylacetylene (2.2 mL, 15.6 mmol) was added to a solution of **(±)-46** (730 mg, 3.2 mmol) in toluene (35 mL). The resulting mixture was heated to reflux for 88 h and then allowed to cool and concentrated under reduced pressure to afford a mixture of **(±)-47** and **(±)-48**. This mixture was used directly in the next step without characterization.

(±)-*tert*-Butyl *trans*-3-Hydroxy-4-(1*H*-1,2,3-triazol-1-yl)-pyrrolidine-1-carboxylate [(±)-48]. The mixture of **(±)-47** and **(±)-48** was taken up in THF (20 mL), and TBAF (4.8 mL, 4.8 mmol, 1 M solution in THF) was added. The reaction mixture was stirred for 4 h, and then further TBAF (1.6 mL, 1.6 mmol, 1 M solution in THF) was added. The mixture was stirred for a further 16 h and then partitioned between EtOAc (30 mL) and water (30 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (2 × 50 mL). The combined organic phases were washed with brine (2 × 50 mL), dried

($MgSO_4$), filtered, and concentrated under reduced pressure. Flash chromatography of the residue (100% EtOAc) afforded (±)-**48** as a pale yellow gum (510 mg, 63%, over 2 steps) and recovered (±)-**47** as a pale yellow oil (140 mg, 14%). (±)-**48**. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.63 (d, J = 6.8 Hz, 1H), 7.58 (s, 1H), 5.44 (br s, 1H), 4.93−4.89 (m, 1H), 4.60 (d, J = 15.9 Hz, 1H), 4.00 (dd, J = 9.5, 7.2 Hz, 1H), 3.77−3.67 (m, 2H), 3.36 (dd, J = 11.8, 4.6 Hz, 1H), and 1.38 ppm (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.4, 154.2 (rotamers), 133.6, 123.1, 80.4, 74.2, 73.4 (rotamers), 65.4, 64.9 (rotamers), 51.7, 51.1 (rotamers), 48.8, 48.4 (rotamers), and 28.4 ppm. ESI-HRMS for $C_{11}H_{18}N_4O_3Na$ $[MNa]^+$ calcd, 277.1277; found, 277.1275. (±)-**47**. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.51 (s, 1H), 4.92−4.78 (m, 2H), 4.49 (br s, 1H), 4.10−4.03 (m, 1H), 3.89−3.79 (m, 2H), 3.44 (br s, 1H), 1.47 (s, 9H) and 0.29 ppm (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.6, 155.4 (rotamers), 147.7, 129.5, 81.5, 75.5, 74.6 (rotamers), 66.5, 66.0 (rotamers), 52.6, 52.1 (rotamers), 50.2, 49.7 (rotamers), 29.6, and 0.0 ppm. ESI-HRMS for $C_{14}H_{26}N_4O_3NaSi$ $[MNa]^+$ calcd, 349.1672; found, 349.1669.

(±)-*trans*-3-Hydroxy-4-(1*H*-1,2,3-triazol-1-yl)pyrrolidine [(±)-49]. Aqueous HCl (36%, 1 mL, 33 mmol) was added to a solution of (±)-**48** (500 mg, 2.0 mmol) in methanol (25 mL). The reaction mixture was concentrated under reduced pressure and subsequently azeotroped with methanol (2 × 20 mL) followed by toluene (10 mL). Flash chromatography of the residue (5:4.6:0.4, CH_2Cl_2/MeOH/28% aqueous NH_4OH) afforded (±)-**49** as an off-white foam (185 mg, 61%). ^{1}H NMR (500 MHz, CD_3OD): δ = 8.06 (d, J = 0.9 Hz, 1H), 7.75 (d, J = 0.9 Hz, 1H), 4.94−4.91 (m, 1H), 4.54−4.51 (m, 1H), 3.58 (dd, J = 12.5, 7.3 Hz, 1H), 3.37−3.34 (m, 1H), 3.27 (dd, J = 12.6, 4.7 Hz, 1H), and 2.92 ppm (dd, J = 12.2, 3.9 Hz, 1H). ^{13}C NMR (125 MHz, CD_3OD): δ = 134.5, 125.4, 78.7, 69.8, 54.7, and 52.3 ppm. ESI-HRMS for $C_6H_{11}N_4O$ $[MH]^+$ calcd, 155.0933; found, 155.0931.

(±)-*trans*-1-[(9-Deazaadenin-9-yl)methyl]-3-hydroxy-4-(1*H*-1,2,3-triazol-4-yl)pyrrolidine [(±)-50]. Formaldehyde (75 μL, 0.9 mmol, 37 wt % solution in water) followed by 9-deazaadenine (100 mg, 0.75 mmol) was added to a solution of (±)-**49** (96 mg, 0.62 mmol) in 1,4-dioxane (1.5 mL) and water (1.5 mL). After being stirred for 66 h the reaction mixture was absorbed onto silica and eluted down a silica column with a gradient of 10−20% (7 N NH_3 in MeOH) in CH_2Cl_2. The crude product was collected, concentrated, and subjected to flash chromatography (5:4.98:0.02, CH_2Cl_2/MeOH/28% aqueous NH_4OH) to afford (±)-**50** (58 mg, 31%). A sample was purified by preparative HPLC to analytical purity as a TFA salt. ^{1}H NMR (500 MHz, CD_3OD): δ = 8.45 (s, 1H), 8.14 (d, J = 0.8 Hz, 1H), 8.08 (s, 1H), 7.80 (d, J = 0.7 Hz, 1H), 5.33 (dt, J = 7.3, 2.8 Hz, 1H), 4.82 (s, 2H), 4.66 (quin, J = 2.2 Hz, 1H), 4.33 (dd, J = 13.2, 7.5 Hz, 1H), 4.15 (dd, J = 13.2, 3.6 Hz, 1H), 3.92 (dd, J = 12.4, 4.5 Hz, 1H), and 3.66 ppm (dd, J = 12.3, 1.7 Hz, 1H). ^{13}C NMR (125 MHz, CD_3OD): δ = 152.0, 145.1, 139.9, 136.1, 135.1, 126.6, 114.1, 104.6, 75.8, 66.6, 60.3, 57.2, and 49.9 ppm (resonance signals due to CF_3COOH have not been quoted). ESI-HRMS for $C_{13}H_{17}N_8O$ $[MH]^+$ calcd, 301.1525; found, 301.1530.

(±)-*tert*-Butyl *trans*-4-Ethynyl-3-hydroxypyrrolidine-1-carboxylate [(±)-51]. Tetrabutylammonium fluoride (3 mL, 3 mmol, 1.0 M solution in THF) was added dropwise to a stirred solution of (±)-**42** (569 mg, 2 mmol) in THF (15 mL). After being stirred for 1 h at room temperature, the reaction mixture was quenched by the addition of water (100 mL) and then extracted with EtOAc (3 × 75 mL). The combined organic phase was washed with brine (80 mL) and then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford crude (±)-**51** as a yellow oil (420 mg, 99%). No further purification was necessary. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.26 (dd, J = 8.4, 3.8 Hz, 1H), 3.63−3.56 (m, 2H), 3.39−3.32 (m, 1H), 3.22 (t, J = 11.5 Hz, 1H), 2.83 (br s, 1H), 2.11 (br s, 1H), and 1.37 ppm (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.7, 82.7, 79.9, 75.0, 74.2 (rotamers), 71.3, 52.3, 52.1 (rotamers), 49.7, 49.2 (rotamers), 37.8, 37.2 (rotamers), and 28.4 ppm. ESI-HRMS for $C_{11}H_{17}NO_3Na$ $[MNa]^+$ calcd, 234.1106; found, 234.1108.

(±)-*tert*-Butyl *trans*-4-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-3-hydroxypyrrolidine-1-carboxylate [(±)-52]. Sodium ascorbate (14 mg, 0.07 mmol) and then copper(II) sulfate (20 μL, 0.02 mmol, 1.0 M aqueous solution) were added to a solution of (±)-**51** (122 mg, 0.6 mmol) and benzyl azide (111 mg, 0.8 mmol) in *t*-BuOH (1 mL) and water (1 mL). After being stirred at room temperature for 18.5 h, the mixture was partitioned between water (10 mL) and EtOAc (10 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (2 × 20 mL). The combined organic phases were washed with 5% aqueous NH_4OH solution (2 × 20 mL) and brine (20 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Flash chromatography of the residue (gradient 50−100% EtOAc in Petrol) afforded (±)-**52** as a yellow oil (114 mg, 57%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34−7.30 (m, 4H), 7.22−7.21 (m, 2H), 5.44 (s, 2H), 4.43 (br d, J = 38 Hz, 1H), 4.18 (d, J = 11.0 Hz, 1H), 3.83 (dd, J = 11.0, 7.6 Hz, 1H), 3.67−3.58 (m, 1H), 3.51−3.44 (m, 1H), 3.41−3.33 (m, 1H), 3.29−3.25 (m, 1H), and 1.40 ppm (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.6, 154.5 (rotamers), 147.2, 147.0 (rotamers), 134.5, 129.1, 128.8, 128.1, 120.9, 79.6, 74.9, 74.1 (rotamers), 54.2, 52.2, 51.9 (rotamers), 49.1, 48.6 (rotamers), 43.5, 43.0 (rotamers), and 28.5 ppm. ESI-HRMS for $C_{18}H_{24}N_4O_3Na$ $[MNa]^+$ calcd, 367.1746; found, 367.1747.

(±)-*trans*-4-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-3-hydroxypyrrolidine [(±)-53]. Aqueous HCl (36%, 500 μL, 16 mmol) was added to a solution of (±)-**52** (114 mg, 0.3 mmol) in methanol (10 mL). The reaction mixture was concentrated under reduced pressure and then azeotroped with methanol (2 × 20 mL) followed by toluene (10 mL). Flash chromatography of the residue (20% (7N NH_3 in MeOH) in CH_2Cl_2) afforded (±)-**53** as an off-white solid (60 mg, 74%). ^{1}H NMR (500 MHz, CD_3OD): δ = 7.81 (s, 1H), 7.38−7.31 (m, 5H), 5.55 (s, 2H), 4.36 (dt, J = 5.7, 3.9 Hz, 1H), 3.43 (dd, J = 11.4, 7.8 Hz, 1H), 3.29−3.25 (m, 1H), 3.14 (dd, J = 12.1, 5.7 Hz, 1H), 2.97 (dd, J = 11.4, 6.5 Hz, 1H), and 2.85 ppm (dd, J = 12.0, 3.7 Hz, 1H). ^{13}C NMR (125 MHz, CD_3OD): δ = 149.8, 136.8, 130.0, 129.6, 126.2, 123.1, 78.9, 55.1, 54.9, 52.4, and 46.8 ppm. ESI-HRMS for $C_{13}H_{17}N_4O$ $[MH]^+$ calcd, 245.1402; found, 245.1401.

(±)-*trans*-4-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-1-[(9-deazaadenin-9-yl)methyl]-3-hydroxypyrrolidine [(±)-54]. Formaldehyde (35 μL, 0.44 mmol, 37 wt % solution in water) followed by 9-deazaadenine (40 mg, 0.30 mmol) was added to a solution of (±)-**53** (60 mg, 0.25 mmol) in 1,4-dioxane (0.6 mL) and water (1.2 mL). The reaction mixture was stirred at room temperature for 17 h, and then further formaldehyde (20 μL, 0.25 mmol, 37 wt % solution in water) was added. After being stirred for 60 h, the reaction mixture was absorbed onto silica and eluted down a silica column with a gradient of 10−30% (7 N NH_3 in MeOH) in CH_2Cl_2. The crude product was collected, concentrated, and subjected to flash chromatography (5:4.9:0.1, CH_2Cl_2/MeOH/28% aqueous NH_4OH) to afford (±)-**54** as an off-white solid (49 mg, 51%). ^{1}H NMR (500 MHz, CD_3OD): δ = 8.14 (s, 1H), 7.79 (s, 1H), 7.48 (s, 1H), 7.37−7.29 (m, 5H), 5.53 (s, 2H), 4.33−4.30 (m, 1H), 3.89 (d, J = 13.4 Hz, 1H), 3.84 (d, J = 13.4 Hz, 1H), 3.25−3.21 (m, 1H), 2.96 (dd, J = 10.3, 6.8 Hz, 1H), 2.77 (dd, J = 10.3, 4.0 Hz, 1H), and 2.68−2.65 ppm (m, 1H). ^{13}C NMR (125 MHz, CD_3OD): δ = 152.1, 151.0, 150.3, 147.0, 136.8, 130.0 (2 C), 129.6, 129.1, 123.1, 115.2, 112.7, 77.8, 62.2, 59.4, 54.9, 48.9, and 46.2 ppm. ESI-HRMS for $C_{20}H_{23}N_8O$ $[MH]^+$ calcd, 391.1995; found, 391.1994.

(±)-*tert*-Butyl *trans*-4-[3-(Benzylthio)propyl]-3-hydroxypyrrolidine-1-carboxylate [(±)-55]. 1,1′-Azobis(cyanocyclohexane) (20 mg, 0.08 mmol) was added to a solution of (±)-**37** (245 mg, 1.1 mmol) and benzyl mercaptan (1.9 mL, 16 mmol) in 1,4-dioxane (1.9 mL). The reaction mixture was heated to 90 °C for 22 h, with further 1,1′-azobis(cyanocyclohexane) (32 mg, 0.1 mmol) being added at intervals of 3, 5, and 6 h. The mixture was allowed to cool and concentrated under reduced pressure. Flash chromatography of the residue (1:9 then 1:1, EtOAc/Petrol) afforded a 5:1 mixture

of (±)-**55**/(±)-**37** as a colorless oil (272 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.31−7.22 (m, 5H), 3.96 (br s, 1H), 3.70 (s, 1H), 3.62−6.52 (m, 2H), 3.25−3.16 (m, 1H), 3.03−2.98 (m, 1H), 2.43−2.41 (m, 2H), 2.21−1.95 (m, 2H), 1.61−1.51 (m, 2H), 1.45 (s, 9H), and 1.30−1.24 ppm (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.6, 138.5, 128.8, 128.5, 127.0, 79.4, 75.5, 74.7 (rotamers), 52.8, 52.5 (rotamers), 49.4, 48.9 (rotamers), 45.9, 45.4 (rotamers), 36.4, 35.7 (rotamers), 31.3, 30.6, 28.5, and 27.3 ppm. ESI-HRMS for $C_{19}H_{29}NO_3NaS$ $[MNa]^+$ calcd, 374.1766; found, 374.1761.

(±)-*trans*-**4-[3-(Benzylthio)propyl]-3-hydroxypyrrolidine [(±)-56].** Aqueous HCl (36%, 500 μL, 16 mmol) was added to a solution of (±)-**55**/(±)-**37** (272 mg, 5:1) in methanol (10 mL). The reaction mixture was concentrated under reduced pressure and then azeotroped with methanol (2 × 20 mL) followed by toluene (10 mL). Flash chromatography of the residue (5:4.6:0.4, CH_2Cl_2/MeOH/28% aqueous NH_4OH) afforded (±)-**56** as a yellow oil (115 mg, 60% over two steps). ^{1}H NMR (500 MHz, CD_3OD): δ = 7.33−7.28 (m, 4H), 7.23−7.20 (m, 1H), 4.14 (s, 1H), 3.72 (s, 2H), 3.53−3.49 (m, 1H), 3.38−3.35 (m, 1H), 3.14 (d, J = 12.3 Hz, 1H), 2.96 (dd, J = 11.6, 5.5 Hz, 1H), 2.47−2.44 (m, 2H), 2.16 (br s, 1H), 1.64−1.50 (m, 3H), and 1.39−1.32 ppm (m, 1H). ^{13}C NMR (125 MHz, CD_3OD): δ = 140.3, 130.0, 129.5, 128.0, 75.1, 52.5, 49.9, 47.0, 37.1, 32.1, 31.2, and 28.5 ppm. ESI-HRMS for $C_{14}H_{22}NOS$ $[MH]^+$ calcd, 252.1422; found, 252.1417.

(±)-*trans*-**4-[3-(Benzylthio)propyl]-1-[(9-deazaadenin-9-yl)-methyl]-3-hydroxypyrrolidine [(±)-57].** Formaldehyde (40 μL, 0.5 mmol, 37 wt % solution in water) followed by 9-deazaadenine (46 mg, 0.3 mmol) was added to a solution of (±)-**56** (75 mg, 0.3 mmol) in 1,4-dioxane (0.8 mL) and water (0.8 mL). After being stirred for 16 h, the reaction mixture was absorbed onto silica and eluted down a silica column with a gradient of 5−50% (7 N NH_3 in MeOH) in CH_2Cl_2. The crude product was collected, concentrated, and subjected to flash chromatography (5:4.95:0.05 then 5:4.8:0.2, CH_2Cl_2/MeOH/28% aqueous NH_4OH) to afford (±)-**57** as an off-white solid (23 mg, 20%). ^{1}H NMR (500 MHz, CD_3OD): δ = 8.16 (s, 1H), 7.48 (s, 1H), 7.30−7.23 (m, 4H), 7.18−7.15 (m, 1H), 3.83−3.79 (m, 3H), 3.67 (s, 2H), 3.00 (t, J = 8.3 Hz, 1H), 2.74 (dd, J = 10.4, 6.4 Hz, 1H), 2.67 (dd, J = 10.3, 4.0 Hz, 1H), 2.38 (t, J = 7.0 Hz, 1H), 2.13 (dd, J = 9.6, 8.0 Hz, 1H), 1.92−1.86 (m, 1H), 1.97−1.48 (m, 3H), and 1.37−1.30 ppm (m, 1H). ^{13}C NMR (125 MHz, CD_3OD): δ = 152.1, 151.0, 147.0, 140.3, 130.1, 130.0, 129.4, 127.8, 115.2, 112.6, 77.6, 62.4, 59.5, 49.1, 48.2, 36.9, 33.4, 32.2, and 28.9 ppm. ESI-HRMS for $C_{21}H_{28}N_5OS$ $[MH]^+$ calcd, 398.2015; found, 398.2013.

(3*R*,4*R*)-*tert*-Butyl 4-(Benzoyloxymethyl)-3-hydroxypyrrolidine-1-carboxylate [(3*R*,4*R*)-59].[40] A solution of (**3*R*,4*R*)-58**[37] (4.10 g, 19 mmol) and dibutyltin oxide (5.17 g, 21 mmol) in toluene (60 mL) was refluxed in a Dean−Stark apparatus for 1 h and then cooled to 5 °C. Benzoyl chloride (2.2 mL, 19 mmol) was added dropwise while the internal temperature was kept below 10 °C. After being stirred at room temperature for 17 h, the reaction mixture was concentrated under reduced pressure. Flash chromatography of the residue (40% EtOAc in Petrol) afforded (**3*R*,4*R*)-59** as a yellow oil (2.48 g, 41%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.03 (d, J = 7.6 Hz, 2H), 7.58 (t, J = 7.4 Hz, 1H), 7.47−7.44 (m, 2H), 4.41−4.37 (m, 1H), 4.35−4.26 (m, 2H), 3.76−3.67 (m, 2H), 3.36−3.25 (m, 2H), 2.60−2.52 (m, 1H), 2.10 (br s, 1H), and 1.46 ppm (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.6, 154.6, 133.2, 129.7, 129.6, 128.5, 79.7, 72.1, 71.4 (rotamers), 64.1, 64.0 (rotamers), 52.7, 52.5 (rotamers), 46.9, 46.4 (rotamers), 45.7, 45.2 (rotamers), and 28.5 ppm.

(3*R*,4R)-*tert*-Butyl 4-(benzoyloxymethyl)-3-(*tert*-butyldimethylsilyloxy)pyrrolidine-1-carboxylate [(3*R*,4*R*)-60].[40] *tert*-Butylchlorodimethylsilane (2.33 g, 15 mmol) was added to a stirred solution of (**3*R*,4*R*)-59** (2.48 g, 7.7 mmol) and imidazole (2.1 g, 31 mmol) in DMF (4 mL). After 17 h the reaction mixture was diluted with toluene (50 mL) and water (50 mL). The phases were separated, and the aqueous phase was extracted with toluene (2 × 50 mL). The combined organic phases were washed with water (2 × 50 mL) and brine (2 × 50 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford (**3*R*,4*R*)-60** as a yellow oil (3.31 g, 99%). No further purification was required. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.03−8.01 (m, 2H), 7.60−7.56 (m, 1H), 7.47−7.43 (m, 2H), 4.37−4.33 (m, 1H), 4.28−4.20 (m, 2H), 3.73−3.57 (m, 2H), 3.33−3.17 (m, 2H), 2.51 (quin, J = 6.3 Hz, 1H), 1.46 (s, 9H), 0.85 (s, 9H), and 0.05 ppm (s, 6H).

(3*R*,4R)-*tert*-Butyl 3-(*tert*-Butyldimethylsilyloxy)-4-(hydroxymethyl)pyrrolidine-1-carboxylate [(3*R*,4*R*)-61].[40] Sodium methoxide (1.8 mL, 7.9 mmol, 25 wt % in methanol) was added to a solution of (**3*R*,4*R*)-60** (3.31 g, 7.6 mmol) in methanol (10 mL). The reaction mixture was stirred at room temperature for 3 h and then diluted with chloroform (40 mL). The mixture was washed with water (2 × 20 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Flash chromatography of the residue (60% EtOAc in Petrol) afforded (**3*R*,4*R*)-61** as a yellow oil (1.2 g, 47%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.20−4.14 (m, 1H), 3.71−3.51 (m, 4H), 3.18−3.10 (m, 2H), 2.31−2.23 (m, 1H), 1.46 (s, 9H), 0.88 (s, 9H), 0.08 (s, 3H), and 0.07 ppm (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.6, 79.4, 72.8, 72.1 (rotamers), 62.5, 62.4 (rotamers), 53.2, 52.5 (rotamers), 48.9, 48.3 (rotamers), 46.4, 45.9 (rotamers), 28.5, 25.8 (rotamers), 17.9, −4.7, and −4.9 ppm.

(3*R*,4*S*)-*tert*-Butyl 3-(*tert*-Butyldimethylsilyloxy)-4-formylpyrrolidine-1-carboxylate [(3*R*,4*S*)-62].[40] Alcohol (**3*R*,4*R*)-61** (1.1 g, 3.3 mmol) was added to a suspension of Dess−Martin periodinane (1.54 g, 3.6 mmol) in CH_2Cl_2 (30 mL), and the reaction mixture was stirred at room temperature for 2.5 h. The reaction mixture was diluted with ether (150 mL) and washed with a 1:1 solution of saturated aqueous sodium hydrogen carbonate solution:10% aqueous sodium thiosulfate solution (2 × 100 mL) and then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Flash chromatography of the residue (1:9 then 2:8, EtOAc/Petrol) afforded (**3*R*,4*S*)-62** as a pale yellow oil (980 mg, 90%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.67 (s, 1H), 4.54−4.52 (m, 1H), 3.68−3.53 (m, 3H), 3.19 (br s, 1H), 2.96 (br s, 1H), 1.43 (s, 9H), 0.86 (s, 9H), and 0.06 ppm (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 199.7, 154.2, 79.8, 71.5, 70.9 (rotamers), 59.1, 58.4 (rotamers), 53.6, 53.0 (rotamers), 43.5, 28.4, 25.6, 17.9, −4.8, and −4.9 ppm.

(3*R*,4*S*)-*tert*-Butyl 3-(*tert*-Butyldimethylsilyloxy)-4-vinylpyrrolidine-1-carboxylate [(3*R*,4*S*)-63]. *n*-Butyllithium (4.3 mL, 6.8 mmol, 1.6 M solution in hexanes) was added dropwise to a stirred suspension of methyltriphenylphosphonium bromide (2.44 g, 6.8 mmol) in THF (10 mL) at 0 °C. After 30 min the suspension was added to a solution of (**3*R*,4*S*)-62** (977 mg, 3.0 mmol) in THF (10 mL) at −78 °C. After being stirred at −78 °C for 1 h, the reaction mixture was warmed to room temperature, stirred for 2.5 h, and then quenched with water (30 mL) and extracted with CH_2Cl_2 (100 mL). The combined organic phases were washed with saturated aqueous sodium hydrogen carbonate solution (50 mL) and brine (50 mL) and then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Flash chromatography of the residue (1:9, EtOAc/Petrol) afforded (**3*R*,4*S*)-63** as a colorless oil (867 mg, 89%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.67 (ddd, J = 17.2, 10.4, 7.8 Hz, 1H), 5.13−5.07 (m, 2H), 3.99 (q, J = 5.9 Hz, 1H), 3.64−3.49 (m, 2H), 3.22−3.07 (m, 2H), 2.67−2.60 (m, 1H), 1.45 (s, 9H), 0.86 (s, 9H), and 0.04 ppm (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.5, 136.6, 116.8, 79.3, 75.8, 74.8 (rotamers), 52.8, 52.3 (rotamers), 50.8, 50.0 (rotamers), 48.5, 48.0 (rotamers), 28.5, 25.7, 18.0, and −4.8 ppm. ESI-HRMS for $C_{17}H_{33}NO_3NaSi$ $[MNa]^+$ calcd, 350.2127; found, 350.2128.

(3*R*,4*S*)-*tert*-Butyl 3-(*tert*-Butyldimethylsilyloxy)-4-ethylpyrrolidine-1-carboxylate [(3*R*,4*S*)-65]. Palladium (100 mg, 0.9 mmol, 10 wt % on carbon) was added to a solution of (**3*R*,4*S*)-63** (870 mg, 2.7 mmol) in ethanol (25 mL) under an argon atmosphere. The reaction mixture was placed under a hydrogen atmosphere and stirred for 15 h and then filtered through Celite and concentrated under reduced pressure to afford (**3*R*,4*S*)-65** (770

mg, 88%). No further purification was necessary. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.90 (d, J = 5.4 Hz, 1H), 3.59 (br s, 1H), 3.54−3.48 (m, 1H), 3.08 (br s, 1H), 3.00−2.94 (m, 1H), 1.90 (br s, 1H), 1.45 (s, 9H), 1.23−1.13 (m, 2H), 0.93 (t, J = 7.5 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 3H), and 0.05 ppm (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.7, 79.1, 75.5, 74.8 (rotamers), 53.4, 52.6 (rotamers), 49.0, 48.5(rotamers), 48.3, 47.6 (rotamers), 28.5, 25.7, 24.3, 18.0, 12.2, −4.7, and −4.8 ppm. ESI-HRMS for $C_{17}H_{35}NO_3NaSi$ $[MNa]^+$ calcd, 352.2284; found, 352.2288.

(3*R*,4*S*)-4-Ethyl-3-hydroxypyrrolidine [(3*R*,4*S*)-67]. A solution of **(3*R*,4*S*)-65** (770 mg, 2.3 mmol) in trifluoroacetic acid (20 mL, 260 mmol) was stirred at room temperature for 17 h and then concentrated under reduced pressure. The residue was dissolved in water (50 mL) and washed with chloroform (2 × 50 mL). The aqueous phase was absorbed onto silica and eluted down a silica column (5:4.5:0.5, CH_2Cl_2/MeOH/28% aqueous NH_4OH) to afford **(3*R*,4*S*)-67** as a yellow oil (205 mg, 76%). ^{1}H NMR (500 MHz, CD_3OD): δ = 3.96 (dt, J = 5.4, 3.5 Hz, 1H), 3.26 (dd, J = 11.4, 7.6 Hz, 1H), 3.01 (dd, J = 12.1, 5.4 Hz, 1H), 2.82 (dd, J = 12.0, 3.4 Hz, 1H), 2.55 (dd, J = 11.4, 6.2 Hz, 1H), 1.91−1.84 (m, 1H), 1.55−1.46 (m, 1H), 1.33−1.24 (m, 1H), and 0.97 ppm (t, J = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, CD_3OD): δ = 77.7, 54.4, 51.3, 50.7, 26.1, and 12.8 ppm. ESI-HRMS for $C_6H_{14}NO$ $[MH]^+$ calcd, 116.1075; found, 116.1080. $[\alpha]_D^{21}$ +5.04 (*c* 1.15, MeOH).

(3*R*,4*S*)-1-[(9-Deazaadenin-9-yl)methyl]-4-ethyl-3-hydroxypyrrolidine [(3*R*,4*S*)-69]. Formaldehyde (53 μL, 0.7 mmol, 37 wt % solution in water) followed by 9-deazaadenine (54 mg, 0.4 mmol) was added to a solution of **(3*R*,4*S*)-67** (44 mg, 0.38 mmol) in 1,4-dioxane (0.7 mL) and water (1.4 mL). The reaction mixture was stirred at room temperature for 66 h, absorbed onto silica, and eluted down a silica column using a gradient 5−30% (7 N NH_3 in MeOH) in CH_2Cl_2. The crude product was collected, concentrated, and subjected to flash chromatography (5:4.5:0.5, CH_2Cl_2/MeOH/28% aqueous NH_4OH) to afford **(3*R*,4*S*)-69** as an off-white solid (67 mg, 67%). ^{1}H NMR (500 MHz, CD_3OD): δ = 8.15 (s, 1H), 7.49 (s, 1H), 3.86−3.77 (m, 3H), 3.06 (dd, J = 9.5, 8.2 Hz, 1H), 2.75 (dd, J = 10.4, 6.3 Hz, 1H), 2.69 (dd, J = 10.4, 4.0 Hz, 1H), 2.18 (dd, J = 9.7, 7.9 Hz, 1H), 1.91−1.84 (m, 1H), 1.59−1.50 (m, 1H), 1.38−1.28 (m, 1H), and 0.92 ppm (t, J = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, CD_3OD): δ = 152.1, 151.0, 147.0, 130.1, 115.1, 112.6, 77.4, 62.4, 59.4, 50.4, 49.2, 27.1, and 12.9 ppm. ESI-HRMS for $C_{13}H_{20}N_5O$ $[MH]^+$ calcd, 262.1668; found, 262.1665. $[\alpha]_D^{21}$ +3.48 (*c* 1.03, MeOH).

(3*R*,4*S*)-*tert*-Butyl-4-(but-1-enyl)-3-(*tert*-butyldimethylsilyloxy)-pyrrolidine-1-carboxylate [(3*R*,4*S*)-64]. *n*-Butyllithium (2.7 mL, 3.8 mmol, 1.4 M solution in hexanes) was added dropwise to a stirred suspension of *n*-propyltriphenylphosphonium bromide (1.743 g, 4.52 mmol) in THF (20 mL) at 0 °C. After 20 min the suspension was cooled to −40 °C and a solution of **(3*R*,4*S*)-62** (497 mg, 1.5 mmol) in THF (10 mL) was added and the resulting mixture was allowed to warm to −10 °C and kept at that temperature for 30 min. The reaction mixture was then quenched with water (50 mL) and extracted with ethyl acetate (50 mL). The organic layer was separated and washed with water (50 mL) and brine (50 mL) and then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Flash chromatography of the resulting residue (1:19, EtOAc/Petrol) afforded **(3*R*,4*S*)-64** as an oil (300 mg, 56%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.51 (dt, J = 10.8, 7.3 Hz, 1H), 5.10 (br t, J = 10.1 Hz, 1H), 3.99−3.91 (m, 1H), 3.67−3.58 (m, 1H), 3.56−3.49 (m, 1H), 3.17−2.89 (m, 3H), 2.17 − 2.00 (m, 2H), 1.45 (s, 9H), 0.97 (t, J = 7.6 Hz, 3H), 0.87 (s, 9H), and 0.04 ppm (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.6, 135.0, 127.6, 79.3, 76.3, 75.6 (rotamers), 53.0, 52.5 (rotamers), 49.6, 49.2 (rotamers), 45.2, 44.5 (rotamers), 28.6, 25.8, 21.0, 18.1, 14.4, and −4.8 ppm. ESI-HRMS for $C_{19}H_{37}NNaO_3Si$ $[MNa]^+$ calcd, 378.2440; found, 378.2438.

(3*R*,4*S*)-4-Butyl-3-hydroxypyrrolidine [(3*R*,4*S*)-68]. A suspension of **(3*R*,4*S*)-64** (260 mg, 0.73 mmol) and Pearlman's catalyst (50 mg, cat., 20% b/w) in ethanol (5 mL) was stirred under an atmosphere of hydrogen at room temperature for 18 h. The reaction mixture was then filtered through Celite and concentrated under reduced pressure to afford, presumably, (3*R*,4*S*)-*tert*-butyl-4-(butyl)-3-(*tert*-butyldimethylsilyloxy)pyrrolidine-1-carboxylate **[(3*R*,4*S*)-66]** as a colorless oil. ^{1}H NMR confirmed the absence of any olefinic protons, and compound **(3*R*,4*S*)-66** was committed to the next step without further characterization or purification. Aqueous HCl (36%, 1 mL, 12 mmol) was added to a solution of **(3*R*,4*S*)-66** (270 mg, 0.76 mmol) in methanol (2 mL) and the resulting solution concentrated under reduced pressure. The resulting residue was dissolved in 36% aqueous HCl (1 mL, 12 mmol) and concentrated under reduced pressure and the resulting residue partitioned between water (10 mL) and $CHCl_3$ (5 mL). The water layer was washed again with $CHCl_3$ (5 mL) and concentrated under reduced pressure to afford the hydrochloride salt of **(3*R*,4*S*)-68** as a white foam (136 mg, 100%). ^{1}H NMR (500 MHz, D_2O): δ = 4.18−4.14 (m, 1H), 3.47 (dd, J = 11.9, 7.4 Hz, 1H), 3.34 (dd, J = 12.7, 5.3 Hz, 1H), 3.11 (dd, J = 12.7, 2.9 Hz, 1H), 2.93 (dd, J = 11.9, 6.1 Hz, 1H), 2.16−2.08 (m, 1H), 1.42−1.31 (m, 1H), 1.25−1.14 (m, 5H) and 0.75 ppm (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, D_2O): δ = 73.9, 51.1, 48.9, 45.3, 30.1, 29.1, 21.9, and 13.3 ppm. ESI-HRMS for $C_8H_{18}NO$ $[MH]^+$ calcd, 144.1388; found, 144.1383.

(3*R*,4*S*)-4-Butyl-1-[(9-deazaadenin-9-yl)methyl]-3-hydroxypyrrolidine [(3*R*,4*S*)-70]. Formaldehyde (86 μL, 1.1 mmol, 37 wt % solution in water) followed by 9-deazaadenine (112 mg, 0.84 mmol) was added to a solution of **(3*R*,4*S*)-68** (100 mg, 0.56 mmol) in 1,4-dioxane (1 mL) and water (2 mL). The reaction mixture was warmed to 85 °C, and after 1 h the crude reaction mixture was absorbed onto silica and eluted down a silica column using a gradient 5−30% (7 N NH_3 in MeOH) in CH_2Cl_2. The crude product was collected, concentrated, and subjected to flash chromatography (5:4.5:0.5, CH_2Cl_2/MeOH/28% aqueous NH_4OH) to afford **(3*R*,4*S*)-70** as an off-white solid (90 mg, 56%). ^{1}H NMR (500 MHz, CD_3OD): δ = 8.17 (s, 1H), 7.49 (s, 1H), 3.86−3.83 (m, 1H), 3.81 (q, J = 13.2 Hz, 2H), 3.05 (dd, J = 9.6, 8.0 Hz, 1H), 2.74 (dd, J = 10.4, 6.3 Hz, 1H), 2.69 (dd, J = 10.4, 4.0 Hz, 1H), 2.17 (dd, J = 9.7, 8.0 Hz, 1H), 1.98−1.90 (m, 1H), 1.57−1.47 (m, 1H), 1.34−1.24 (m, 5H), and 0.89 ppm (t, J = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, CD_3OD): δ = 152.1, 151.0, 147.0, 130.1, 115.1, 112.6, 77.8, 62.4, 59.7, 49.1, 48.6, 34.0, 31.5, 23.8, and 14.4 ppm. ESI-HRMS for $C_{15}H_{24}N_5O$ $[MH]^+$ calcd, 290.1981; found, 290.1988.

(±)-Benzyl *cis*-3-(Benzoyloxy)-4-ethylpyrrolidine-1-carboxylate [(±)-71]. Benzoic acid (430 mg, 3.5 mmol) and triphenylphosphine (909 mg, 3.5 mmol) were added to a stirred solution of **(±)-12** (719 mg, 2.8 mmol) in THF (24 mL). The reaction mixture was cooled to −10 °C, and DIAD (680 μL, 3.5 mmol) was added dropwise over 10 min. After being stirred at −10 °C for 45 min, the reaction mixture was warmed to room temperature and stirred for 22 h and then concentrated under reduced pressure. Flash chromatography of the residue (1:9 then 2:8, EtOAc/Petrol) afforded **(±)-71** as a pale colorless oil (995 mg, 98%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.12−8.00 (m, 2H), 7.60−7.56 (m, 1H), 7.49−7.28 (m, 7H), 5.57−5.53 (m, 1H), 5.20−5.09 (m, 2H), 3.89−3.67 (m, 3H), 3.29 (dt, J = 19.1, 10.7 Hz, 1H), 2.35−2.24 (m, 1H), 1.68−1.46 (m, 2H), and 0.98−0.94 ppm (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.0, 165.9, 154.8, 136.9, 136.7, 133.5, 133.3, 133.2, 130.2, 130.0, 129.9, 129.7, 128.5, 128.4, 127.9, 74.7, 73.8 (rotamers), 67.0, 66.9 (rotamers), 53.3, 53.0 (rotamers), 49.8, 49.5 (rotamers), 45.1, 44.3 (rotamers), 20.1, and 12.4 ppm. ESR-HRMS for $C_{21}H_{23}NO_4Na$ $[MNa]^+$ calcd, 376.1525; found, 376.1521.

(±)-Benzyl *cis*-4-Ethyl-3-hydroxypyrrolidine-1-carboxylate [(±)-72]. A solution of K_2CO_3 (583 mg, 4.2 mmol) in water (20 mL) was added to a solution of **(±)-71** (995 mg, 2.8 mmol) in ethanol (40 mL). The resulting mixture was heated to reflux for 90 min and then allowed to cool and was concentrated under reduced pressure. The residue was partitioned between DCM (50 mL) and water (50 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (3 × 50 mL).

The combined organic phases were washed with brine (2 × 50 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Flash chromatography of the residue (3:7, EtOAc/Petrol) afforded (±)-**72** as a yellow oil (476 mg, 68%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35−7.29 (m, 5H), 5.15−5.08 (m, 2H), 4.23 (br s, 1H), 3.67−3.47 (m, 3H), 3.14 (dd, J = 10.8, 3.6 Hz, 1H), 2.24 (br d, J = 45 Hz, 1H), 2.01−1.94 (m, 1H), 1.61−1.53 (m, 1H), 1.51−1.43 (m, 1H), and 0.98−0.94 ppm (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.2, 155.0, 136.9, 128.4, 127.9, 127.8, 71.7, 70.7 (rotamers), 66.8, 66.7 (rotamers), 55.5, 55.0 (rotamers), 49.0, 48.8 (rotamers), 46.0, 45.3 (rotamers), 19.6, and 12.4 ppm. ESI-HRMS for $C_{14}H_{19}NO_3Na$ $[MNa]^+$ calcd, 272.1263; found, 272.1268.

(±)-***cis*-4-Ethyl-3-hydroxypyrrolidine [(±)-73].** Palladium (10 mg, 0.01 mmol, 10 wt % on carbon) was added to a solution of (±)-**72** (146 mg, 0.5 mmol) in MeOH (10 mL) under argon. The reaction mixture was placed under a hydrogen atmosphere and stirred for 1 h and then filtered through Celite and concentrated under reduced pressure. Flash chromatography of the residue (gradient 10−40% (7 N NH_3 in MeOH) in DCM) afforded (±)-**73** as a yellow oil (42 mg, 62%). ^{1}H NMR (500 MHz, CD_3OD): δ = 4.17 (td, J = 4.5, 1.4 Hz, 1H), 3.04 (dd, J = 12.2, 4.4 Hz, 1H), 2.99 (dd, J = 10.5, 7.9 Hz, 1H), 2.84 (dd, J = 12.2, 1.3 Hz, 1H), 2.61 (t, J = 10.6 Hz, 1H), 1.86−1.79 (m, 1H), 1.65−1.56 (m, 1H), 1.46−1.37 (m, 1H), and 0.98 ppm (t, J = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, CD_3OD): δ = 73.2, 56.0, 50.6, 48.6, 21.0, and 13.3 ppm. ESI-HRMS for $C_6H_{14}NO$ $[MH]^+$ calcd, 116.1075; found, 116.1077.

(±)-***cis*-1-[(9-Deazaadenin-9-yl)methyl]-4-ethyl-3-hydroxypyrrolidine [(±)-74].** Formaldehyde (35 μL, 0.4 mmol, 37 wt % solution in water) followed by 9-deazaadenine (52 mg, 0.4 mmol) was added to a solution of (±)-**73** (32 mg, 0.3 mmol) in 1,4-dioxane (1 mL) and water (1 mL). The reaction mixture was stirred at room temperature for 68 h, absorbed onto silica, and eluted down a silica column using a gradient 10−50% (7 N NH_3 in MeOH) in CH_2Cl_2. The crude product was collected, concentrated, and subjected to flash chromatography (5:4.9:0.1 then 5:4.8:0.2, CH_2Cl_2/MeOH/28% aqueous NH_4OH) to afford (±)-**74** as an off-white solid (45 mg, 62%). ^{1}H NMR (500 MHz, CD_3OD): δ = 8.16 (s, 1H), 7.49 (s, 1H), 4.20 (td, J = 5.8, 3.3 Hz, 1H), 3.89 (s, 2H), 3.17 (dd, J = 10.9, 5.5 Hz, 1H), 2.95 (dd, J = 9.4, 7.5 Hz, 1H), 2.57 (dd, J = 10.9, 3.3 Hz, 1H), 2.41 (t, J = 9.9 Hz, 1H), 2.00−1.92 (m, 1H), 1.61−1.53 (m, 1H), 1.38−1.28 (m, 1H), and 0.92 ppm (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, CD_3OD): δ = 152.1, 151.0, 147.0, 130.1, 115.1, 112.7, 72.5, 63.0, 58.3, 49.4, 46.6, 21.4, and 13.2 ppm. ESI-HRMS for $C_{13}H_{20}N_5O$ $[MH]^+$ calcd, 262.1668; found, 262.1663.

Protein Expression and Inhibition Assays. *E. coli* MTAN and human MTAP used in the biological evaluation of the compounds were expressed as IPTG-inducible His-tagged recombinant enzymes purified using Ni-NTA chromatography. Enzyme inhibition assays were carried out using a xanthine oxidase-coupling enzyme that converts the adenine product of the MTAN and MTAP reactions to 2,8-dihydroxyadenine monitored at 293 nm (ε_{293} = 15.2 mM^{-1} cm^{-1}). The 1 mL reaction mixture consisted of 100 mM HEPES, pH 7.4, 50 mM KCl, 250 μM MTA, 100 mM potassium phosphate (only for the MTAP reaction), and varying concentrations of inhibitor, in the presence of xanthine oxidase (Sigma). The reaction was initiated by addition of 4 nM *E. coli* MTAN or 10 nM human MTAP and monitored for 60−90 min at 25 °C. Controls without inhibitor and without enzyme were included in the experiment. K_i values were determined using the following equation for competitive inhibition:

$$v'_0/v_0 = \frac{K_m + [S]}{K_m + [S] + \frac{K_m[I]}{K_i}}$$

where v'_0 and v_0 are initial rates in the presence and absence of inhibitor, respectively; K_m and [S] are the Michaelis constant and concentration of MTA, respectively, and K_i and [I] are the inhibition constant and inhibitor concentration, respectively. If [I] is less than 10 times the enzyme concentration, the following correction is applied:

$$I' = I - \left(1 - \frac{v'_0}{v_0}\right) E_t$$

where I' is the effective inhibitor concentration to be used in the equation for competitive inhibition above, and E_t is the final enzyme concentration. In some instances, a second slower rate phase is observed in progress curves of tight binding inhibitors. These steady state rates are taken instead (v'_s/v_s) and used in the inhibition equation above to determine the overall inhibition constant K_i*, which reflects the slow onset inhibition of the enzyme−inhibitor complex.

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