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Total Synthesis of Q Base (Queuine)

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Abstract—The total synthesis of Q Base (Queuine) has been accomplished in eleven steps from ribose. Mitsunobu reaction of nosyl protected amine **12** with known cyclopentenol **7**, derived from ribose, gave **13**, the first key intermediate in the synthesis. The pyrrolo[2,3-*d*]pyrimidine ring system of Q Base was built via a cyclocondensation reaction between a β-aminobromoaldehyde **16**, derived from the Mitsunobu product **13**, and 2,4-diamino-6-hydroxypyrimidine. Deprotection of the product from the cycloccondensation reaction (**17**) gave Q Base.

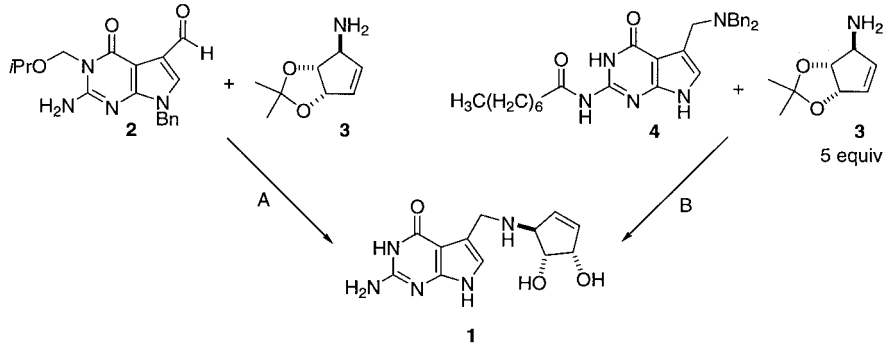
Introduction

Q Base (**1**), also known as queuine, is found in the tRNA of both plants and animals. Isolated and identified in the 1970's, much work has been undertaken to understand the biological function of **1**.[1] Of particular interest is the fact that the tRNA isolated from various tumors was found to be deficient in Q Base. Administration of Q Base in one tumor cell line in mice was found to inhibit tumor growth.[2] There continues to be an interest in the biological role of Q Base, as much is still not understood.[3]

Two syntheses of Q Base (**1**) have been reported to date. The two approaches are outlined in Scheme 1. Route A was reported by Kondo, et al. in 1983.[4] The key step in this synthesis was the formation of the Schiff base of aldehyde **2** and cyclopentylamine **3**[5] and reduction of this species to give a protected version of **1.** Deprotection of this product gave Q Base (**1**) in a total of 19 steps. Route B was reported by Akimoto, et al. in 1988.[6] The strategy of their synthesis was to use an amine exchange between pyrrolopyrimidine **4** and amine **3** to obtain the desired product. This route suffers from the requirement of five equivalents of **3**, also obtained from a multistep synthesis,[5] to drive the reaction to completion. We would like to report here the total synthesis of Q Base (**1**) via a new route utilizing a different disconnection.

Results and Discussion

Scheme 2 outlines our retrosynthetic approach to the synthesis of Q Base (**1**). Based on work we recently reported,[7] we envisioned that the pyrrolopyrimidine ring system could be constructed from the cyclocondensation of 2,4-diamino-6-hydroxypyrimidine (**5**) and a bromoaldehyde such as **6**.[8] We then hypothesized that bromoaldehyde **6** might be derived



Scheme 1. Previous approaches to the synthesis of Q Base (**1**).

Keywords: Q Base; cyclocondensation; pyrrolopyrimidine.

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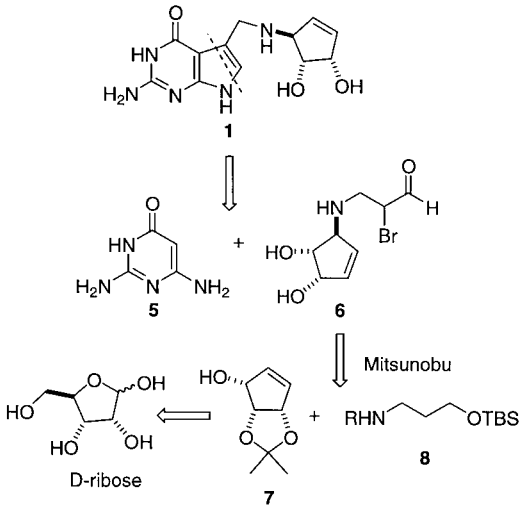
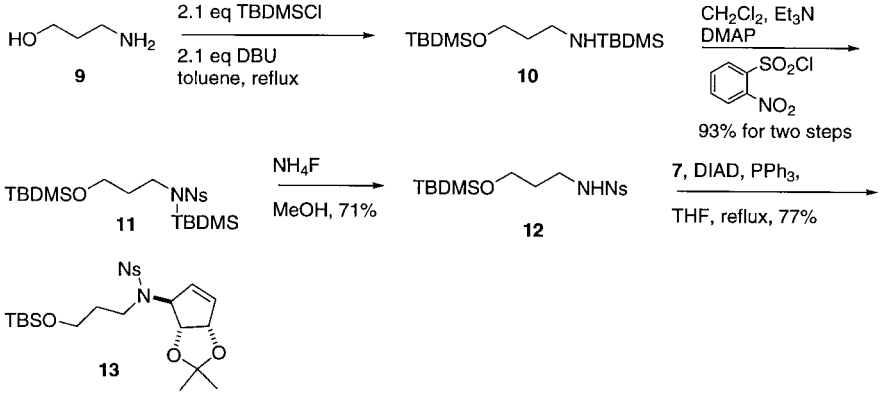


Scheme 2. Retrosynthetic analysis of Q Base (**1**).

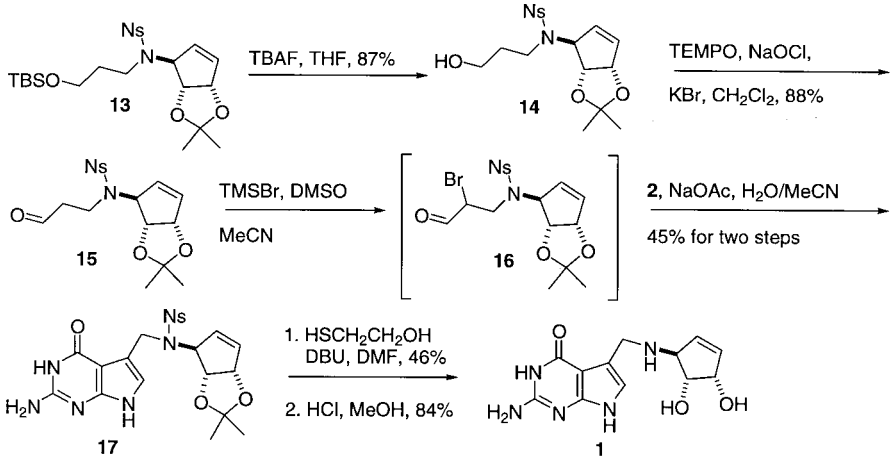
from a Mitsunobu reaction between known cyclopentenol **7**, available in four steps from ribose,[9] and a suitably protected nitrogen intermediate **8**. This approach would allow construction of Q Base (**1**) in a sequence of eleven linear steps from ribose. The choice of nitrogen protecting group for **8** would affect two synthetic steps: Mitsunobu reaction of **8** with **7** and bromination of the aldehyde needed to obtain **6**. In our previous work we determined that the *o*-nitrophenylsulfonyl (*o*-Ns) group provided sufficient stabilization of bromoaldehyde products similar to **6** to allow for their isolation and cyclocondensation to form pyrrolopyrimidines.[7] Additionally, recent work in the area of Mitsunobu reactions has shown that *o*-Ns amides work well in reactions with alcohols in a manner similar to that needed in our construction.[10] Thus the *o*-Ns group was chosen for our synthesis.

Synthesis of the protected amine piece for the Mitsunobu reaction was carried out as shown in Scheme 3. Bis-silylation of 3-amino-1-propanol (**9**) was achieved by reaction of **9** with 2.1 equiv. of TBDMSCl and DBU[11] to give amine **10**. Protection of the nitrogen of **10** as a sulfonamide using *o*-nosyl chloride in CH_2Cl_2 gave fully protected amide **11** in 93% yield for the two steps. Selective removal of the silyl group from nitrogen using NH_4F in MeOH[12] gave nosyl amine **12** in 71% yield. Mitsunobu coupling of amine **12** was carried out with alcohol **7** using diisopropyl azodicarboxylate (DIAD) and PPh_3 in THF at reflux for 24 h. Conditions were optimized using those from Mitsunobu reactions of nosyl amines[10] and reactions reported using alcohol **7**.[13] It was determined that a slight excess of alcohol **7** (about 1.2 equiv) was needed to ensure complete reaction and allow for purification of the product. If unreacted amide **12** remained, it was difficult to separate it from the desired product (**13**). The stereochemical outcome of the Mitsunobu reaction was expected to be complete inversion at the center where displacement takes place. This is predicted by the outcome of reactions of **7**[13] reported previously, but was also confirmed independently in our labs. Synthesis of alcohol **14**, derived from known amine **3**,[5] was carried out as outlined in our earlier work and optical rotations of alcohol **14** obtained from the different routes were compared.[14] Values were in good agreement and no diastereomers were observed by NMR, confirming that the Mitsunobu reaction had proceeded cleanly with inversion. No products from other possible competing mechanisms (S_N1 or S_N2') were detected.

Completion of the synthesis of Q Base (**1**) from Mitsunobu product **13** is shown in Scheme 4. Desilyation of the oxygen using TBAF in THF gave alcohol **14** in 87% yield. 2,2,6,6-tetramethyl-1-piperidinyloxy free radical (TEMPO) oxidation[15] of **14** provided aldehyde **15** in 88% yield. Bromination of **15** using TMSBr and DMSO (1 equiv. each) in acetonitrile[16] was followed by immediate condensation with 2,3-diamino-6-hyrdoxypyrimidine[17] to give cyclized product **17** in 45% yield for the two steps. Bromoaldehyde **16** proved to be unstable and the duration of the bromination reaction was critical for its success. ^{1}H NMR analysis was used to determine the exact time needed for the bromination reaction to reach completion. Longer reaction times led to decomposition. Concentration was also very important in this reaction. If the reaction mixtures were too dilute, bromination proceeded very slowly and was accompanied by appreciable decomposition of the product. It should also be noted that the method of bromination used in our synthesis of **1** differs from that employed in our methodolgy studies.[7] This change is due to the increased sensitivity of substrate **16** and product **17**. By employing the TMSBr and DMSO in MeCN conditions we were able to perform a one pot bromination and cyclocondensation reaction without the need to isolate unstable bromide **16**.



Scheme 3. Synthesis of nosyl amine and Mitsunobu reaction.



Scheme 4. Completion of synthesis of Q Base (**1**).

Completion of the synthesis of Q Base required only the removal of the two protecting groups on **17**. While efficient methods were found to remove both the nosyl[18] and the acetonide groups,[4] significant challenges arose in the purification of these products. Both compounds were quite insoluble in most organic solvents, with MeOH and EtOH being exceptions. No acceptable conditions were found that would allow for crystallization, and ultimately, chromatography was utilized. Thus with polar eluents (mixtures of EtOAc/EtOH/NH_4OH, see Experimental) denosylated **17** and Q Base (**1**) were obtained in good purity. ^1H and ^{13}C NMR data for **1** obtained by this synthesis agreed with that reported for **1**.[19] Optical rotation data for Q Base obtained from our synthesis were also in good agreement with the published data,[4] further confirming that the stereochemical outcome of the Mitsunobu reaction was as predicted.

Conclusion

We have achieved the synthesis of Q Base by a new route, utilizing a Mitsunobu reaction and subsequent cyclocondensation reaction to build the core structures. The synthesis is straightforward and efficient. A new entry into the construction of this class of molecules has been made which expands the possible synthetic approaches available.

Experimental

Materials and methods

Reagents and solvents were used as received from the supplier. Reactions were carried out under an atmosphere of nitrogen with magnetic stirring. ^1H and ^{13}C NMR spectra were collected at 300 MHz and 75 MHz respectively and acquired in $CDCl_3$ unless otherwise noted. TLC was carried out on glass plates, precoated with silica gel 60. Column chromatography was carried out using Silica gel 60, 230–400 mesh.

***N,O*-Bis(*tert*-butyldimethylsilyl)-3-amino-1-propanol (10).** To a solution of 3-amino-1-propanol (**9**) (10.0 g, 133.1 mmol) in toluene (200 mL) were added DBU (42.0 mL, 280.8 mmol) and TBDMSCl (42.52 g, 282.1 mmol). After refluxing for 2 h, the solution was washed with water. The aqueous phase was extracted with Et_2O and the combined organic phases dried over $MgSO_4$, filtered and concentrated under reduced pressure to give 41.1 g crude bis-TBS protected aminopropanol **10** as a colorless oil. This material was characterized by ^1H NMR and used without further purification. A small sample was purified by vacuum (2–3 mm Hg) distillation for characterization. ^1H NMR: δ 0.04 (s, 6H), 0.05 (s, 6H), 0.89 (s, 9H), 0.91 (s, 9H), 1.63–1.70 (m, 2H), 2.77–2.84 (m, 2H), 3.63–3.71 (m, 2H). ^{13}C: δ −5.3, −3.4, 18.1, 18.3, 25.8, 26.0, 36.2, 39.4, 61.3.

***N,O*-Bis(*tert*-butyldimethylsilyl)-*N*-*o*-nitrobenzenesulfonyl-3-amino-1-propanol (11).** To a solution of bis-TBS compound **10** (10.1 g, 33.3 mmol) in CH_2Cl_2 (100 mL) were added Et_3N (7.0 mL, 50.2 mmol), *o*-nitrobenzenesulfonyl chloride (8.05 g, 36.3 mmol), and DMAP (50–100 mg, catalytic). The solution stirred for 3 h and then washed sequentially with 1N HCl (50 mL), saturated $NaHCO_3$ (50 mL), and saturated NaCl (50 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give 15.11 g (30.9 mmol, 93% yield) of nosylate **11** as a yellow oil. This material was used directly in the next reaction without further purification. The ^1H NMR spectrum indicated that partial *N*-desilylation had occurred during the sulfonylation reaction. ^1H NMR: δ 0.05 (s, 6H), 0.10 (s, 6H), 0.87 (s, 9H), 0.91 (s, 9H), 1.6–1.75 (m, 2H), 3.20–3.26 (m, 2H), 3.67 (m, 2H), 7.71–7.74 (m, 2H), 7.83–7.86 (m, 1H), 8.11–8.14 (m, 1H).

***N*-*o*-Nitrobenzenesulfonyl-*O*-*tert*-butyldimethylsilyl-3-amino-1-propanol (12).** To a solution of nosylate **11** (30.8 g, 63.0 mmol) in MeOH (400 mL) was added NH_4F (2.57 g, 69.4 mmol). The solution was stirred for 30 min before H_2O (50 mL) was added and the solution concentrated under reduced pressure. The residue was taken up in Et_2O (300 mL) and washed sequentially with H_2O (2×75 mL) and saturated NaCl solution (50 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give 19.8 g (52.9 mmol, 84%) of crude **12** as a yellow oil. Purification by column chromatography (10–30% EtOAc/hexanes) gave 16.7 g

(44.6 mmol, 71% yield) of sulfonamide **12** as a viscous yellow oil. IR (cm^{-1}, film) 3400, 2956, 2930, 2858, 1544, 1410, 1362, 1169, 1096, 838. ^1H NMR: δ 0.03 (s, 6H), 0.85 (s, 9H), 1.72 (quint, J=6.2 Hz, 2H), 3.21 (q, J=5.6 Hz, 2H), 3.67 (t, J=5.6 Hz, 2H), 5.72 (t, J=5.6 Hz, 1H), 7.69–7.73 (m, 2H), 7.81–7.84 (m, 1H), 8.08–8.11 (m, 1H). ^{13}C NMR: δ −5.4, 18.3, 25.9, 31.8, 41.9, 61.1, 125.1, 130.9, 132.5, 133.4, 147.9. HRMS: calcd for $C_{15}H_{27}N_2O_5SSi$ 375.1410, found 375.1404.

(1*S*,2*R*,3*S*)-*N*-(3-*tert*-Butyldimethylsilyloxypropyl)-*N*-(*o*-nitrobenzenesulfonyl)-2,3-isopropylidinedioxycyclopent-4-enylamine (13); Mitsunobu reaction of 7 and 12. To a stirred solution of alcohol **7**[9] (4.20g, 26.9 mmol) in THF (50 mL) was added a solution of amine **12** (8.09 g, 21.6 mmol) in THF (50 mL). Triphenylphosphine (10.56 g, 40.3 mmol) was added. To the mixture was added a solution of DIAD (8.0 mL, 40.6 mmol) in THF (10 mL) dropwise over 10–15 min. The solution was refluxed for 24 h, cooled to room temperature, and filtered through a plug of silica gel. The plug was eluted with Et_2O (200–300 mL) and the filtrate concentrated under reduced pressure to give 31.60 g of a yellow oil. Careful chromatography (elution with 10–50% CH_2Cl_2/hexanes, followed by CH_2Cl_2) gave 8.55 g (77%) of pure **13** as a yellow viscous oil. IR (cm^{-1}, film) 2956, 2931, 2858, 1546, 1373, 1258, 1166, 1097, 1051, 938, 837. ^1H NMR: δ 0.02 (s, 6H), 0.86 (s, 9H), 1.28 (s, 3H), 1.39 (s, 3H), 1.64–1.85 (m, 1H), 3.00–3.10 (m, 1H), 3.33 (ddd, J=5.3 Hz, 10.6 Hz, 15.2 Hz, 1H), 3.57 (t, J=5.6 Hz, 2H), 4.50 (d, J=5.9 Hz, 1H), 4.90 (d, J= 1.8 Hz, 1H), 5.20–5.23 (m, 1H), 6.02 (ddd, J= 1.8 Hz, a.8, 5.6 Hz, 1H), 7.65–7.73 (m, 3H), 8.06–8.12 (m, 1H). ^{13}C NMR: δ −5.3, 14.2, 18.3, 21.7, 22.7, 25.6, 25.9, 27.3, 31.6, 33.9, 43.9, 70.4, 83.1, 84.2, 111.5, 123.9, 131.0, 133.2, 133.5, 136.6, 147.9. HRMS: calcd for $C_{23}H_{40}N_3O_7SSi$ M+NH_4 530.2356, found 530.2366. $[\alpha]_D^{23}$=+36.7° (c=1.09, MeOH).

(1*S*,2*R*,3*S*)-*N*-(3-Hydroxypropyl)-*N*-(*o*-nitrobenzenesulfonyl)-2,3-isopropylidinedioxycyclopent-4-enylamine (14). To a solution of silyl alcohol **13** (2.61 g, 5.1 mmol) in THF (50 mL) was added TBAF (1.0 M solution in THF, 6.6 mL, 6.6 mmol). The solution was stirred until TLC indicated complete consumption of starting material (2–3 h). The solution was diluted with Et_2O, washed successively with water and saturated NaCl solution, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give crude alcohol **14**. Chromatography on silica gel (20–50% EtOAc/hexanes, followed with EtOAc) gave 1.77 g (87%) of pure alcohol **14** as a yellow oil. IR (cm^{-1} thin film) 3050, 2950, 1546, 1373, 1163, 1050. ^1H NMR: δ 1.21 (s, 3H), 1.31 (s, 3H), 1.63–1.72 (m, 2H), 2.51 (br s, 1H), 3.07 (dt, J=7.3, 15.0 Hz, 1H), 3.33–3.43 (m, 1H), 3.58 (t, J=5.8 Hz, 2H), 4.44 (d, J=5.8 Hz, 1H), 4.80 (d, J=1.0 Hz, 1H), 5.17–5.19 (m, 1H), 5.59–5.62 (m, 1H), 5.97–5.99 (m, 1H), 7.57–7.72 (m, 3H), 87.97–8.03 (m, 1H). ^{13}C NMR: δ 14.1, 21.0, 25.4, 27.1, 33.1, 43.7, 59.0, 60.3, 70.4, 83.0, 111.3, 123.9, 130.5, 131.0, 131.6, 132.7, 133.7, 136.5, 147.6. HRMS: calcd for $C_{17}H_{21}N_2O_7S$+Na 421.1045, found 421.1033. $[\alpha]_D^{23}$=+35.2° (c=0.95, MeOH).

(1*S*,2*R*,3*S*)-*N*-(3-Oxopropyl)-*N*-(*o*-nitrobenzenesulfonyl)-2,3-isopropylidinedioxycyclopent-4-enylamine (15). Oxidation of alcohol **14** was carried out according to the procedure in Ref. [15]. Thus 1.63 g (4.1 mmol) of alcohol **14** was treated with 2,2,6,6-tetramethyl-1-piperidinyloxy free radical (TEMPO) (15.7 mg, 0.10 mmol), KBr (85.3 mg, 0.72 mmol) and NaOCl (5.25% solution, 6.7 mL, diluted with one volume water containing 463 mg $NaHCO_3$) to give 1.23 g (3.1 mmol, 88% yield) of aldehyde **15** as a yellow oil after workup. This material was used directly as obtained without further purification. ^1H NMR: δ 1.28 (s, 3H), 1.39 (s, 3H), 2.77–2.87 (m 2H), 3.22 (ddd, J=6.7, 8.8, 14.4 Hz, 1H), 3.65 (ddd, J=6.2, 8.7, 15.2 Hz, 1H), 4.43 (d, J=5.9 Hz, 1H), 4.90 (d, J=1.5 Hz, 1H), 5.22–5.24 (m, 1H), 5.66–5.69 (m, 1H), 6.07 (ddd, J=1.8, 2.0, 5.6 Hz, 1H), 7.62–7.77 (m, 3H), 8.08–8.11 (m, 1H), 9.72 (s, 1H). ^{13}C NMR: δ 25.2, 26.9, 39.2, 44.8, 70.5, 82.5, 83.9, 111.5, 123.9, 130.6, 131.3, 131.6, 132.2, 133.9, 137.0, 147.9, 199.4.

2-Amino-5-[(1*S*,2*R*,3*S*)-*N*-(*o*-nitrobenzenesulfonyl)-2,3-isopropylidinedioxycyclopent-4-enylaminomethyl]-pyrrolo[2,3-*d*]pyrimin-4(3*H*)-one (17). A solution of aldehyde **15** (5.2956 g, 13.3 mmol) in acetonitrile (26 mL) was cooled to 0°C. To this solution were added TMSBr (1.8 mL, 13.6 mmol) and DMSO (0.95 mL, 13.4 mmol) via syringe. The ice bath was removed and the solution stirred for 4 h at rt. At that time a solution of 2,4-diamino-6-hydroxypyrimidine (1.65 g, 13.1 mmol) and NaOAc (1.22 g, 14.9 mmol) in water (26 mL), warmed slightly to dissolve all solids, was added to the reaction mixture. After stirring overnight, the reaction mixture was extracted with EtOAc (5×200 mL). The combined organic extracts were washed with water (50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 5.15 g (10.2 mmol, 77%) of crude pyrrolopyrimidine **17** as an orange solid. The crude material was purified by column chromatography, loading as a solution in EtOAc and eluting with the following solvent systems: 1:1 EtOAc/hexanes, followed by 99:0.9:0.1 EtOAc/EtOH/NH_4OH, then 95:4.5:0.5 EtOAc/EtOH/NH_4OH, and finally 90:9:1 EtOAc/EtOH/NH_4OH to give 3.02 g (6.0 mmol, 45% yield) of **17** as a yellow amorphous solid which resisted crystallization. Further purification proved difficult but the material obtained was suitable to carry forward in the synthesis. IR (cm^{-1}, KBr) 3400, 2800, 1699, 1632, 1543, 1164, 1127. ^1H NMR (DMSO-d_6): δ 1.51 (s, 3H), 1.24 (s, 3H), 4.32–4.54 (m, 3H), 4.84–4.89 (m, 2H), 5.54 (dd, J=5.6, 5.9 Hz), 5.87–5.9 (m, 1H), 6.05 (s, 2H), 6.39 (d, J=2.1 Hz, 1H), 7.76–8.03 (m, 4H), 10.24 (s, 1H), 10.88 (d, J=2.1 Hz, 1H). ^{13}C NMR (CD_3OD): δ 25.8, 27.6, 42.7, 71.5, 84.2, 85.6, 99.7, 101.2, 112.3, 116.1, 118.8, 125.2, 131.7, 131.9, 132.8, 134.5, 134.9, 137.4, 149.1, 152.1, 153.8, 161.6. HRMS: calcd for $C_{21}H_{22}N_6O_7S$ (M+1) 503.1349, found 503.1339.

2-Amino-5-[(1*S*,2*R*,3*S*)-2,3-isopropylidinedioxycyclopent-4-enylaminomethyl]pyrrolo[2,3-*d*]pyrimin-4(3*H*)-one. To a solution of **17** (284 mg, 0.57 mmol) in DMF (2.5 mL) were added DBU (180 μL, 1.20 mmol) and β-mercaptoethanol (44 μL, 0.63 mmol).[18] After stirring at rt for 24 h the DMF was removed in vacuo. The residue was taken up in ethanol, silica gel added, and solvent removed under reduced pressure. The resulting dry powder was put on top of a column of silica. Elution of the product was carried out with EtOAc, followed by 95:4.5:0.5 EtOAc/EtOH/NH_4OH to 70:27:3 EtOAc/EtOH/NH_4OH. Concentration

of product containing fractions gave 83.2 mg (0.26 mmol, 46% yield) of denosylated **17** as a yellow solid. The low yield is probably due to loss on chromatography since the reaction appeared to be nearly quantitative by TLC. ^{1}H NMR (CD_3OD): δ 1.31 (s, 3H), 1.33 (S, 3H), 3.78–3.82 (m, 2H), 3.93 (d, J=13.2 Hz, 1H), 4.59 (d, J=5.7 Hz, 1H), 5.23 (d, J=5.0 Hz, 1H), 5.85 (ddd, J=1.1, 2.3, 5.9 Hz, 1H), 5.93 (dd, J=1.5, 5.6 Hz), 6.66 (s, 1H). ^{13}C NMR (CD_3OD): δ 25.8, 27.6, 44.3, 69.4, 84.0, 85.9, 100.1, 112.0, 116.6, 117.3, 134.5, 153.2, 153.9, 162.02. HRMS: calcd for $C_{15}H_{19}N_5O_3$ (M + 1) 318.1566, found 318.1563.

2-Amino-5-[(1*S*,2*R*,3*S*)-2,3-dihyroxycyclopent-4-enyl-aminomethyl]pyrrolo[2,3-*d*]pyrimin-4(3*H*)-one, Q base (1). A solution of de-nosylated **17** (53.7 mg, 0.17 mmol) in 1N HCl (4.5 mL) and MeOH (2.0 mL) was heated at 80°C for 8 h.[4] The solution was cooled and concentrated under reduced pressure. A solution of 9:1 EtOH/NH_4OH (5–6 mL) was added and most solid dissolved. This solution was loaded onto a short column of silica which was packed using hexanes. The column was eluted with hexanes, 1:1 EtOAc/hexanes, 100% EtOAc, 90:9:1 EtOAc/EtOH/NH_4OH, 70:27: 3.0 EtOAc/EtOH/NH_4OH, 50:45:5 NH_4OH/EtOH/EtOAc and then with 9:1 EtOH/NH_4OH. Fractions containing the product were concentrated under reduced pressure to give 39.4 mg of Q Base (**1**) (0.14 mmol, 84%) as a white solid. All spectra matched the published data.[19] ^{1}H NMR (CD_3OD): δ 4.17–4.18 (m, 1H), 4.25–4.29 (m, 1H), 4.34–4.38 (m, 1H), 4.44–4.48(m, 1H), 4.59–4.61 (m, 1H), 6.03–6.06 (m, 1H), 6.22–6.24 (m, 1H), 6.87 (s, 1H). ^{13}C NMR (D_2O, dioxane at 67.4): δ 43.0, 67.3, 73.8, 74.5, 99.1, 108.5, 120.0, 129.8, 138.4, 152.1, 153.4, 161.9. HRMS: calcd for $C_{12}H_{15}N_5O_3$ (M+1) 278.1254, found 278.1253. Optical rotation data was obtained after adding 2.5 equiv. HCl to form the salt, as the literature value was obtained from the HCl salt. Observed $[\alpha]_D^{23}$=+111° (c=0.30, H_2O), lit. $[\alpha]_D^{26}$=+113° (c=0.3, H_2O).[4]

References

1. (a) Hoops, G. C.; Townsend, L. B.; Garcia, G. A. *Biochemistry* **1995**, *34*, 15381–15387. (b) Jaconson, K. B. *Nucleosides Nucleotides* **1984**, *3*, 91–107. (c) Reyniers, J. P.; Farkas, W. R. *Anal. Biochem.* **1983**, *130*, 427–430. (d) Crain, P. F.; Sethi, S. K.; Katze, J. R.; McCloskey, J. A. *J. Biol. Chem.* **1980**, *255*, 8405–8407.

2. Katze, J. R.; Beck, W. T. *Biochem. Biophys. Res. Commun.* **1980**, *96*, 313.

3. (a) Kersten, H. *Biofactors* **1988**, *1*, 27–29. (b) Kinzie, S. D.; Thern, B.; Iwata-Reuyl, D. *Org. Lett.* **2000**, *2*, 1307–1310.

4. Kondo, T.; Ohgi, T.; Goto, T. *Chem. Lett.* **1983**, 419–422.

5. (a) Tanaka, K.; Ogasawara, K. *Synthesis* **1996**, 219–222. (b) Fang, J.; Chering, Y. *J. Chem. Res., Miniprint* **1986**, 1564–1572. (c) Oghi, T.; Goto, T. *Tetrahedron Lett.* **1976**, *17*, 367–370.

6. Akimoto, H.; Imamiya, E.; Hitaka, T.; Nomura, H. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1637–1644.

7. Barnett, C. J.; Grubb, L. M. *Tetrahedron Lett.*, in press.

8. (a) Secrist, J. A.; Liu, P. S. *J. Org. Chem.* **1978**, *43*, 3937–3941. (b) Noell, C. W.; Robins, R. K. *J. Heterocycl. Chem.* **1964**, *1*, 34–41. (c) Migawa, M. T.; Hinkley, J. M.; Joops, G. C.; Townsend, L. B. *Synth. Commun.* **1996**, *26*, 3317–3322.

9. (a) Ali, S. M.; Ramesh, K.; Borchardt, R. T. *Tetrahedron Lett.* **1990**, *31*, 1509–1512. (b) Borcherding, D. R.; Scholtz, S. A.; Borchardt, R. T. *J. Org. Chem.* **1987**, *52*, 5457–5461. (c) Seley, K. L.; Schneller, S. W.; Rattendi, D.; Lane, S.; Bacchi, C.J. *Antimicrob. Agents Chemother.* **1997**, *41*, 1658–1661.

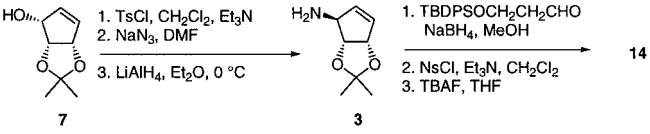
10. (a) Fukuyama, T.; Cheung, M.; Kan, T. *Synlett* **1999**, 1301–1303. (b) Fukuymam, T.; Cheung, M.; Jow, C-K.; Hidai, Y.; Kan, T. *Tetrahedron Lett.* **1997**, *38*, 5831–5834. (c) Fukuyama, T.; Jow, C-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373–6374.

11. Hart, D. J.; Grillot, A. *Heterocycles* **1994**, *39*, 435–438.

12. Williams, D. M.; Brown, D. M. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1225–1231.

13. (a) Seley, K. L.; Schneller, S. W.; Korba, B. *J. Med. Chem.* **1998**, *41*, 2168–2170. (b) Seley, K. L.; Schneller, S. W.; Rattendi, D.; Lane, S.; Bacchi, C. J. *J. Med. Chem.* **1997**, *40*, 625–629. See also Ref. [9c].

14. Synthesis was carried out similarly to that reported for cyclopentylamine examples reported in Ref. [7]. The exact route is outlined here:



15. Anelli, P. L.; Montanari, F.; Quici, S. *Org. Synth.* **1990**, *69*, 212–219.

16. Bellesia, F.; Ghelfi, F.; Grandi, R.; Pagnoni, U. M. *J. Chem. Res., Synop.* **1986**, 428–429.

17. Barnett, C. J.; Wilson, T. M.; Kobierski, M. E. *Org. Process Res. Dev.* **1999**, *3*, 184–188.

18. Miller, S. C.; Scanlan, T. S. *J. Am. Chem. Soc.* **1997**, *119*, 2301–2302.

19. Sierzputowska-Gracz, H.; Agris, P. F.; Katze, J. R. *Magn. Reson. Chem.* **1988**, *26*, 4–7. See also Ref. [4].