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An enantioselective synthesis of the cyclopentene fragment of nucleoside Q

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Abstract—An enantioselective synthesis of (3*S*,4*R*,5*S*)-(+)-3-amino-4,5-dihydroxycyclopentene, a segment of nucleoside Q and Q base, is reported utilizing an amino acid-derived acylnitroso Diels–Alder cycloaddition.

Nucleoside Q, **1a**, also known as queuosine, was found to be located in the first position of the anticodon region of *Escherichia coli* tRNA[1] (Fig. 1). Further studies showed that nucleoside Q is widely distributed in tRNA's of both plants and animals.[2] Nucleoside Q and its biosynthetic precursors have potential as biologically active compounds since deficiency of nucleoside Q is related to tumor growth.[2c] However, relatively little is known about their biological role and the molecular mechanisms. Detailed structural analysis of this compound carried out by the Goto group[3] found that nucleoside Q consists of 7-deazaguanosine, the 7-position of which is connected via a methylene bridge to the amino group of (3*S*,4*R*,5*S*)-(+)-3-amino-4,5-dihydroxycyclopentene. The aglycone of nucleoside Q was named Q base, **1b**, and is also known as queuine. In biological systems Q base is known to exist in four forms: free queuine base, free nucleoside, free nucleotide and nucleoside incorporated into tRNA. Interestingly, the tRNA isolated from various tumors was found to be deficient in Q base.[4,5] The biological role of Q base is not fully understood and the study of its function continues.[6] (3*S*,4*R*,5*S*)-(+)-3-Amino-4,5-dihydroxycyclopentene is a common fragment of both nucleoside Q and Q base. Since this fragment is known to play an important role in the exhibition of physiological activity by nucleoside Q,[7] its enantioselective synthesis was investigated.

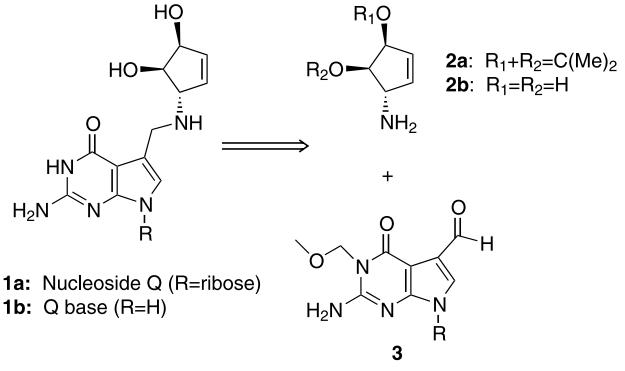

Figure 1.

One of the synthetic routes to nucleoside Q or Q base is the highly efficient condensation[8] to form the Schiff base of the partially protected 7-deazaguanine derivative with (+)-cyclopentenylamine acetonide **2a**, the reduction of which gives the protected nucleoside Q or Q base. However, the disadvantage of this approach is the lack of an efficient route to a suitable dihydroxycyclopentenylamine building block. Reported routes from (±)-dicyclopentadiene are lengthy.[9] In order to more effectively study the biochemical properties of RNA fragments containing Q base or nucleoside Q as well as its derivatives, an efficient route to a dihydroxylcyclopentenylamine building block is desirable. This report provides a convenient and stereoselective route to this compound utilizing an amino acid-derived acylnitroso Diels–Alder cycloaddition. Previously, asymmetric acylnitroso Diels–Alder reactions involving amino acids as chiral auxiliaries were developed in our group and applied to efficient syntheses of novel carbocyclic nucleosides.[10]

Keywords: enantioselective synthesis; nucleoside Q; acylnitroso Diels–Alder cycloaddition.

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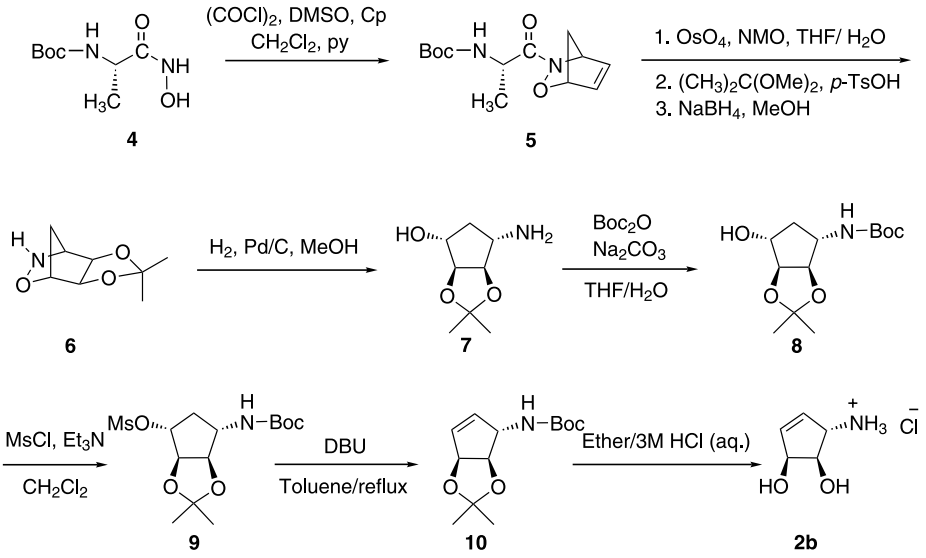
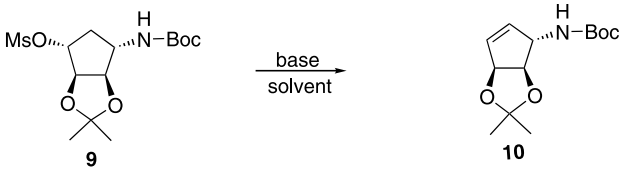


Scheme 1.

The synthetic route to (3*S*,4*R*,5*S*)-(+)-3-amino-4,5-dihydroxycyclopentene **2b** is described in Scheme 1. Hydroxamic acid **4**, readily accessible from L-Ala, was oxidized to the acylnitroso species, which was trapped in situ with cyclopentadiene to produce cycloadduct **5**. Oxidation carried out using $NaIO_4$ in MeOH/water at 0°C resulted in a 3:1 mixture of readily separable diastereomers **5** in 75% combined yield. The same compound was obtained under Swern oxidation conditions at –78°C as a 5:1 mixture of diastereomers in 70% combined yield. The major diastereomer was isolated in 50% yield and its structure is shown in Scheme 1. The stereospecific *exo–cis*-hydroxylation of **5** was achieved using OsO_4 and protection of the resulting diol was accomplished by stirring with a catalytic amount of *p*-TsOH in 2,2-dimethoxypropane as solvent to give the corresponding acetonide. Reductive removal of the amino acid auxiliary occurred under mild conditions, using $NaBH_4$ in MeOH to provide **6** in an enantiomerically pure form. Hydrolysis of simple primary and secondary amides usually requires acidic or basic conditions. This Weinreb-type amide **5** was easily reduced under mild conditions by $NaBH_4$ in methanol to give amine **6**.[11] The nitrogen–oxygen bond in **6** was easily cleaved by hydrogenation utilizing Pd/C in MeOH under an atmosphere of H_2 to provide the amino alcohol **7**. This amino alcohol has been reported as a key intermediate in the synthesis of carbocyclic nucleosides.[12] The spectral data for **7** were in good agreement with those reported earlier.[10] This free amine was treated with Boc_2O in the presence of Na_2CO_3 in THF/H_2O to provide Boc-protected amine **8**. The conversion from **5** to **8** was carried out in 64% yield overall without any chromatographic separation of the intermediates. Compound **8** was converted into the corresponding mesylate **9** in 95% yield by treatment with methanesulfonyl chloride and triethylamine in CH_2Cl_2.[13] A direct base-induced elimination using DBU in toluene produced the desired compound **10** in 76% yield.[13,14]

The effects of base on the regiochemistry of elimination were explored with various bases (Table 1). Treatment of compound **9** with *t*-BuOK resulted in alcohol **8** as the major product although a *syn* elimination product has been previously reported for a similar compound with this base.[15] Treatment of **9** with LiN_3 led to *anti* elimination at C-5 to produce desired compound **10**, however, only 10% conversion was observed. The effect of basicity on this elimination reaction was investigated with bases of various pKa values. Nitrogen containing bases mostly produced compound **10** although the reaction rates were slow. There is no clear correlation between basicity and reaction rate, however, the highest conversion to the desired product **10** was obtained with DBU (pKa 12). The yield is dependent on the concen-

Table 1. Effect of base on elimination reaction of **9**



Base	Conc. **9** (M)	Result[a] (isolated yield)
t-BuOK(5 equiv.)[b]	0.062	See text
LiN_3 (2 equiv.)[c]	0.048	10% conversion to **10**
Pyridine (5 equiv.)	0.050	No reaction
DMAP (2 equiv.)	0.054	33% conversion to **10**
4-Ethylmorpholine (5 equiv.)	0.193	5% conversion to **10**
Et_3N (5 equiv.)	0.066	No reaction
DBU (1.2 equiv.)	0.078	50% conversion to **10** (40%)
DBU (1.2 equiv.)	0.27	75% conversion to **10** (66%)
DBU (1.2 equiv.)	1.35	89% conversion to **10** (76%)

[a] Reactions were heated at reflux for 2 days in toluene and conversion ratios were determined by ^1H NMR integration.
[b] Reaction done in THF at rt for 30 min.
[c] Reaction heated at reflux for 2 days in THF.

tration of **9**, while the relative amount of DBU did not affect the rate or yield of this reaction. Higher concentrations of **9** resulted in a higher yield of **10**; the yield of 76% was obtained when the concentration of **9** was 1.35 M. Compound **2b** was prepared from **10** by treating with dilute aqueous HCl in ether.[13] All the spectral data including the specific optical rotation were in agreement with those reported earlier for the same compound.[9]

In conclusion, we present here an efficient route to synthesize enantiomerically pure **2b**, the side chain of nucleoside Q. The overall yield of **2b** from cycloadduct **5** was 43% and ease of scale up is superior to previously reported syntheses. This improved route to **2b** provides a practical advantage for the preparation of nucleoside Q and its derivatives.

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13. **(1*R*,2*R*,3*R*,4*S*)-1-Methanesulfonyloxy-2,3-dioxyisopropylidene-4-amino-(*tert*-butoxycarbonyl)-1,2,3-cyclopentanetriol** (**9**): Alcohol **8** (0.84 g, 3.00 mmol) was dissolved in CH_2Cl_2 (10 mL) and cooled to 0°C. Triethylamine (1.67 mL, 12.0 mmol) and methanesulfonyl chloride (0.46 mL, 6.00 mmol) were added to the solution. The reaction was allowed to warm to room temperature while the mixture was stirred for 1 h. The mixture was diluted with CH_2Cl_2 followed by washing with water, 1N HCl solution, and brine. The solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give a colorless oil. The crude residue was purified by flash chromatography (20–50% EtOAc/hexanes) to give 1.01 g of white solid in 95% yield. Mp 113–114°C (recrystallized from EtOAc–hexanes); $[\alpha]_D^{20} = -23.8°$ (*c* 3.129, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (s, 3H), 1.41 (s, 3H), 1.44 (s, 9H), 1.98 (d, $J = 15.3$ Hz, 1H), 2.48 (ddd, $J = 5.8$, 6.0, 15.1 Hz, 1H), 3.07 (s, 3H), 4.15 (m, 1H), 4.59 (d, $J = 5.3$ Hz, 1H), 4.72 (dd, $J = 1.4$, 5.6 Hz, 1H), 4.83 (m, 1H), 4.96 (d, $J = 4.5$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.2, 26.5, 28.6, 34.9, 38.7, 56.6, 84.5, 85.8, 86.7, 111.6, 155.2; IR (TF) 3453, 3399, 2981, 2938, 1713, 1504, 1365, 1177 cm^{-1}; LRMS (FAB) *m*/*z* 142, 184, 238, 252, 296, 352 $(M+H)^+$; HRMS (FAB) calcd for $C_{14}H_{26}O_7NS$ $(M+H)^+$ 352.1430, found 352.1446.
(3*S*,4*R*,5*S*)-3-*tert*-Butoxycarbonylamino-4,5-isopropylidenedioxycyclopent-1-ene (**10**): Methanesulfonate **9** (0.95 g, 2.70 mmol) and DBU (0.49 mL, 3.3 mmol) were dissolved in toluene (2 mL) and the resulting mixture was heated to reflux for 2 days. The solvent was removed under reduced pressure using ethyl ether as a co-solvent. The crude residue was purified by flash chromatography (20% EtOAc/hexanes) to give 0.52 g of white solid product in 76% yield and starting material was recovered in 9.8% yield (0.093 g). Mp 92–93°C; $[\alpha]_D^{20} = +102.5°$ (*c* 0.363, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (s, 3H), 1.38 (s, 3H), 1.43 (s, 9H), 4.47 (d, $J = 5.8$ Hz, 2H), 4.58 (br s, 1H), 5.20 (d, $J = 5.8$ Hz, 1H), 5.73–5.76 (m, 1H), 5.95 (d, $J = 5.8$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.0, 27.6, 28.6, 62.7, 84.5, 85.1, 111.7, 132.7, 135.3, 155.3; IR (TF) 3374, 3325, 3058, 2985, 1687, 1520, 1367, 1162 cm^{-1}; LRMS (FAB) *m*/*z* 142, 184, 198, 254, 256 $(M+H)^+$; HRMS (FAB) calcd for $C_{13}H_{22}NO_4$ $(M+H)^+$ 256.1549, found 256.1559.
(3*S*,4*R*,5*S*)-3-Amino-4,5-dihydroxycyclopentene hydrochloride (**2b**): To a solution of the carbamate **10** (0.057 g, 0.22 mmol) in ether (5 mL) was added aqueous HCl (3.0 M, 0.5 mL) at room temperature and the resulting mixture was stirred for 24 h. The solvent was evaporated under reduced pressure and further evacuated under vacuum to give a white foam in 95% yield (30 mg). $[\alpha]_D^{20} = +188.6°$ (*c* 0.300, MeOH); ^{1}H NMR (300 MHz, CD_3OD) δ 4.03 (t, $J = 5.5$ Hz, 1H), 4.08–4.10 (m, 1H), 4.56–4.68 (m, 1H), 5.93 (dd, $J = 6.3$, 1.5 Hz, 1H), 6.19 (ddd, $J = 6.3$, 2.4, 1.8 Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 62.6, 74.5, 76.3, 131.2, 139.2; IR (TF) 3341, 2932, 1605 cm^{-1}; HRMS (FAB) calcd for $C_5H_{10}NO_2$ $(M-Cl)^+$ 116.0712, found 116.0730.
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