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The Asymmetric Synthesis of (3*S*,4*R*,5*S*)-3-Amino-4,5-*O*-isopropylidenedioxycyclopentene

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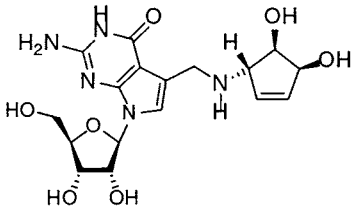
Abstract:

The title amine, an important substructure of nucleoside Q, is available from the 3,4-epoxycyclopentene in five steps. The epoxide is directly converted to the acetonide of *cis*-3, 4-dihydroxycyclopentene by treatment with boron trifluoride, a ring-opening with retention of configuration, a previously unknown process since known conversions of epoxides directly to acetonides normally involve initiating by nucleophilic opening of the epoxide with inversion of configuration. Two strategies were developed for diastereoselective allylic oxidation to *cis*-3,4-*O*-isopropylidenedioxy-*trans*-5-hydroxycyclopentene—direct oxidation with selenium dioxide and a two-step process, epoxidation followed by base. The corresponding carbonate undergoes a palladium-catalyzed deracemization with phthalimide as nucleophile in 98% ee. Recrystallization can increase the ee to >99%. Removal of the phthalimide group to give the title compound occurs smoothly with ethylenediamine. Thus, a most efficient five-step synthesis (six steps from cyclopentadiene) contrasts with two recent asymmetric syntheses that required 12−16 steps.

Nucleoside Q (**1**) has been found widely distributed in the anticodon region of the tRNAs of numerous plants and animals.[1] This unusual nucleoside, also known as queuosine, possesses a deazaguanosine attached to ribose. A (*3S,4R,-5S*)-3-aminocyclopent-1-ene-3,4-diol (**2a**) substructure is



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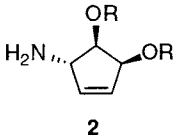

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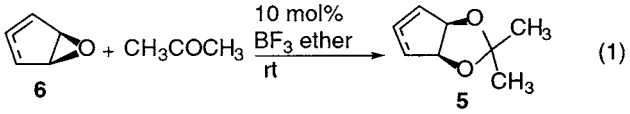
a) R, R = H
b) R, R = $C(CH_3)_2$

attached to the 7-position by a methylene bridge. In a project directed towards the total synthesis of unusual nucleosides, we embarked upon a synthesis of queuosine for which a practical asymmetric synthesis of the aminocyclopentenediol substructure is required.[2] In 1996, a 16-step synthesis from dicyclopentadiene that utilizes an enzymatic resolution was recorded.[3] Two years later a 12-step synthesis involving starting from mannitol, a compound from the chiral pool, was published.[4] In this report, we report a six-step synthesis to the amino diol **2a** from cyclopentadiene that employs a catalytic asymmetric reaction which allows access to either enantiomer with equal facility.

Scheme 1 outlines the retrosynthetic analysis. The deracemization involves formation of pseudomeso π-allylpalladium complex which arises by ionization of both allylic carbonates **4a** and ***ent*-4a**.[5] The term pseudomeso derives from the fact that the complex is not meso when the ligands on the palladium are chiral. However, it behaves as a meso substrate since desymmetrization of the allyl moiety creates the chiral products wherein the regioselectivity of the nucleophilic attack determines which enantiomer of the product forms. Allylic oxidation of the racemic cyclopentene **5** should create the correct diastereomer. Solvolysis of the epoxide **6**, easily derived by epoxidation of cyclopentadiene (**7**), in acetone should create the requisite acetonide.

Conversion of epoxides directly to acetonides normally involves one inversion of configuration—i.e., (*Z*)-epoxides give (*E*)-acetonides.[6] In the present case that entails formation of a strained trans fused bicyclo [3.3.0]octane system. Thus, a cis ring-opening is required. To effect such a process, a S_N1- rather than S_N2- type process is needed wherein ring-opening of the epoxide **6** to an allyl cation occurs. Thus, focus was on stronger Lewis acids. Unfortunately, only complex mixtures resulted upon treating the acetone solution of the epoxide with 10 mol % aluminum chloride or zinc iodide. A Bronsted acid, *p*-toluenesulfonic acid, led to similar results. On the other hand, 10 mol % BF_3-ether[6b] led to direct formation of the acetonide **5**[7] (eq 1) in 73% yield. Yields as high as 83% of the crude product were obtained.



6 **5** (1)

Oxidation of **5** was pursued via two routes (eq 2). In the first route, the exposure of the cyclopentene to selenium

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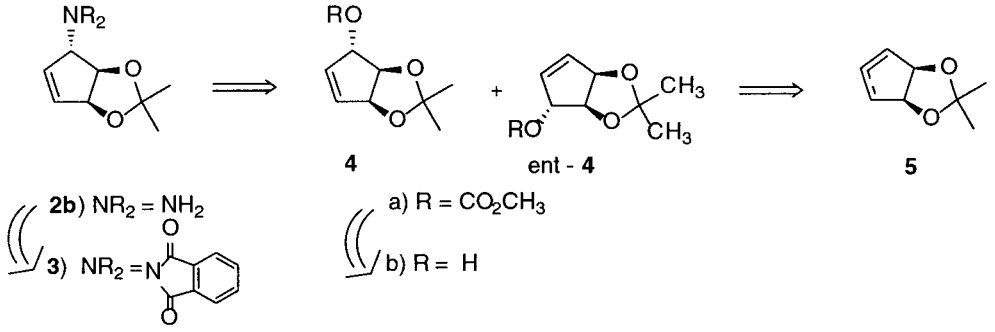
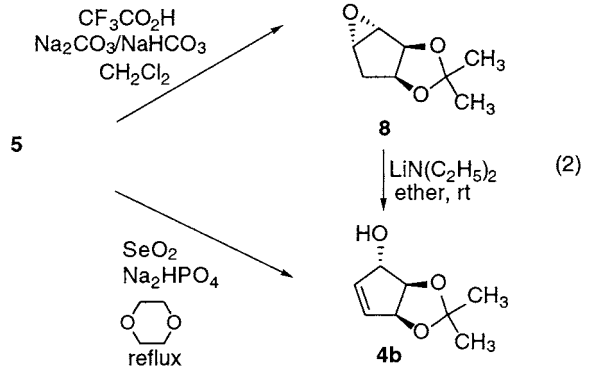
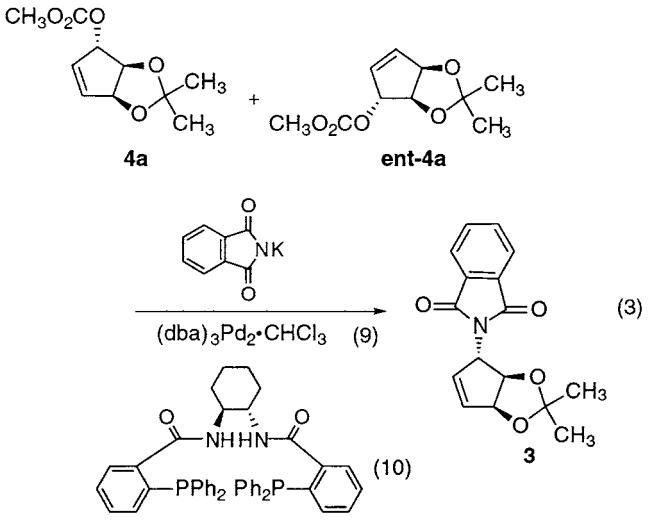
Scheme 1. **Retrosynthetic analysis**



dioxide in hot dioxane[8] gave the desired alcohol racemic **4b** in 68−70% yield. Since the reaction could not be performed

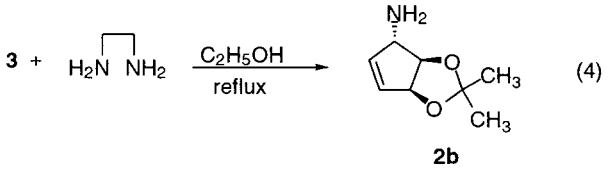


catalytic in selenium dioxide, an alternative was pursued. Epoxidation required a highly electrophilic peracid, trifluoroperacetic acid, which was generated anhydrously by reacting solid urea−hydrogen peroxide complex with trifluoroacetic anhydride.[9] The reaction was buffered with a 3:1 mixture of sodium carbonate: sodium bicarbonate to avoid acid-catalyzed ring-opening of the epoxide. The crude epoxide was directly subject to lithium diethylamide (eq 3) in ether[10] at room temperature to give the same racemic allylic alcohol **4b** in 62% yield for the two steps.



Conversion of the alchohol **4b** to the methyl carbonates **4a** and ***ent*-4a** occurred with methyl chlorocarbonate and pyridine setting the stage for the asymmetric allylic alkylation. Equation 3 and Table 1 outline the results.

The low solubility of potassium phthalimide was mitigated by the addition of tetra-*n*-hexylammonium bromide. This additive also had a significant effect on ee (entry 2).[5,11] Running the reaction at 0° for 6 h and then allowing the temperature to rise to room temperature saw the best ee's (entries 3 and 6). Quenching the reaction at 0° had no effect (entry 5). Addition of water which allows reduction of the amount of the tetraalkylammonium salt gave equivalent results (entry 2 vs 4). Although the yields typically varied between 60 and 70%, no starting material remained. Cleavage of the phthalimide occurred smoothly with ethylenediamine to give the target compound in 78% yield (eq 4). The spectral data agreed with those previously reported.[1a,3,4] Furthermore, the rotation also was in excellent accord with the literature.[1a]



$[\alpha]_D$ + 148.6 (c 0.35, CH_3OH)

lit. $[\alpha]_D$ + 148 (c 0.39, CH_3OH)

The deracemization of **4** and ***ent*-4** requires the Pd to complex to the alkene syn to the acetonide. Thus, the steric bulk of the acetonide might have been thought to hinder the Pd AAA. Indeed, this was a major concern regarding the viability of this method. After completion of this study, the reaction of **4** and ***ent*-4** has also been reported with an *N*-alkylsulfonamide as the nucleophile with our chiral ligands.[12] In that case, a 93% yield of alkylated product of 99.5% ee was obtained. Thus, the yield in the present case most likely derives from the use of potassium phthalimide as nucleophile. Clearly, substrate **4** is an excellent substrate for the Pd deracemization with our ligands. Since the absolute configuration of amine **2b** is known, the absolute configuration of the product using the *S,S* ligand **10** is that depicted. This synthesis of the desired acetonide **2b** requires five steps

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Table 1. **Pd-Catalyzed DYKAT**[a]

entry	solvent	additive	temp (deg)	time (h)	yield (%)	ee (%)
1	THF	none	rt	12	66	57
2	CH_2Cl_2	1 equiv $(C_6H_{13})_4NBr$	rt	12	63	87
3	CH_2Cl_2	1 equiv $(C_6H_{13})_4NBr$	0−rt	16	64	98
4	$CH_2Cl_2-H_2O$	0.1 equiv $(C_6H_{13})_4NBr$	rt	16	60	86
5	CH_2Cl_2	1 equiv $(C_6H_{13})_4NBr$	0	12	61	98
6	CH_2Cl_2	1 equiv $(C_6H_{13})_4NBr$	0−rt	12	62	98

[a] All reactions were performed at 0.1 M in substrate using 2.5 mol % $(dba)_3Pd_2{\cdot}CHCl_3$ and 7.5 mol % ligand **10**.

and proceeds in 17% overall yield from the monoepoxide of cyclopentadiene.

Experimentals

3,4-*cis*-O-Isopropylidenedioxycyclopentene (5). To a stirring solution of cyclopentene oxide (2.0 g, 24.4 mmol) in dry acetone (50 mL) at room temperature was added boron trifluoride etherate (0.35 g, 2.44 mmol). The solution was stirred at room temperature for 6 h. The solution was concentrated in vacuo and the residue taken up in diethyl ether (30 mL), washed with saturated aqueous sodium bicarbonate (3 × 10 mL), saturated aqueous ammonium chloride (3 × 10 mL), and saturated aqueous sodium chloride (3 × 10 mL). The organic layers were dried over sodium sulfate and concentrated in vacuo to give crude acetonide. Distillation at 38−42 °C (3 mmHg) (lit.[7a] bp 148 °C) gave the pure acetonide as a clear, colorless liquid (2.53 g, 73%). Other preparations led to product without purification in crude yields of approximately 83%. IR (neat): 3045, 2923, 1607, 1458, 1420, 1386, 1120 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.83−5.78 (m, 2H), 5.10 (d, J = 6.0 Hz, 1H), 4.76 (t, J = 6.0 Hz, 1H), 2.57−2.53 (m, 2H), 1.41 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.0, 132.2, 111.2 86.9, 79.2, 40.2, 32.3, 27.0.

4,5-*cis*-*O*-Isopropylidenedioxycyclopentene-*trans*-3-ol (4b). *Method 1.* To a solution of **5** (4.0 g, 28.5 mmol), dibasic acid phospate (4.1 g, 28.5 mmol), and dry quartz sand (1.0 g) in dry dioxane (50 mL) was added selenium dioxide (6.3 g, 57.0 mmol) at room temperature. The mixture was heated to reflux and stirred at this temperature overnight. The resulting black mixture was allowed to cool to room temperature and was then filtered through a plug of Celite. The filtrate was concentrated in vacuo and taken up in ethyl acetate (40 mL). This solution was washed with saturated aqueous ammonium chloride (3 × 15 mL), saturated aqueous sodium bicarbonate (3 × 15 mL), and saturated aqueous sodium chloride (3 × 15 mL). The organic layers were dried over sodium sulfate and concentrated in vacuo to give a brown oil. Kugelrohr distillation at 141−151 °C at 1.8 mmHg gave the desired alcohol as a clear, colorless liquid, (3.0 g, 68%). IR (neat): 3416, 3063, 2988, 2935, 1590, 1372, 1210, 1042 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.97 (d, J = 3.0 Hz, 1H), 5.86 (d, J = 3.0 Hz, 1H), 5.23 (d, J = 4.5 Hz, 1H), 4.72 (s, 1H), 4.46 (d, J = 4.5 Hz, 1H), 1.36 (s, 3H), 1.22 (s, 3H). ^{13}C NMR: (75 MHz, $CDCl_3$): δ 136.9, 136.4, 113.3, 87.4, 85.8, 82.3, 28.7, 27.1. HRMS: Calcd for $C_7H_9O_3$ ($M^+ - CH_3$): 141.0552. Found: 141.0553.

Method 2. To a solution of **5** (42.1 mg, 0.3 mmol) in DCM (3 mL) was added sodium bicarbonate (25.2 mg, 0.3 mmol), sodium carbonate (95.4 mg, 0.9 mmol) and urea−hydrogen peroxide (141.1 mg, 1.5 mmol). After cooling to 0 °C, trifluoroacetic anhydride (157.5 mg, 0.75 mmol) was added dropwise. The mixture was stirred at 0 °C for 30 min and was washed with saturated sodium bicarbonate (3 × 1 mL); the organic layers were dried over sodium sulfate and concentrated in vacuo to give crude epoxide **8** (40.0 mg, 85% yield) which was used without further puricification. IR (neat): 2987, 2938, 1374, 1269, 1210, 1160, 1074 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 4.52 (m, 2H), 3.59 (s, 2H), 2.29 (dd, J = 14.2, 6.8 Hz, 1H), 1.95 (dd, J = 14.2, 1.2 Hz, 1H), 1.46 (s, 3H), 1.32 (s, 3H); ^{13} C NMR ($CDCl_3$, 75 MHz): δ 113.4, 82.8, 81.5, 60.5, 60.3, 37.0, 28.5, 26.1. HRMS: Calcd for $C_7H_9O_3$ ($M^+ - CH_3$): 141.0052. Found: 141.0555. Anal. Calcd for $C_8H_{12}O_3$: C 61.52, H 7.74. Found: C 61.50, H 7.91.

A solution of crude epoxide **8** (93.7 mg, 0.6 mmol) in diethyl ether (1.0 mL) was treated with lithium diethyl amide (1.0 M in diethyl ether and hexanes, 1.8 mL, 1.8 mmol) at room temperature. After 4 h, the reaction was quenched with water (0.5 mL). The organic layer was separated and washed with saturated sodium bicarbonate (3 × 0.3 mL), saturated ammonium chloride (3 × 0.3 mL), and saturated sodium chloride (3 × 0.3 mL), dried over sodium sulfate, and concentrated in vacuo. Kugelruhr distillation (at 141−151 °C at 1.8 mm) gave the desired alcohol as a clear, colorless oil (68.0 mg, 62% over two steps).

***trans*-Methoxycarbonyloxy-*cis*-4,5-*O*-isopropylidene-dioxycyclopentene (4a).** To a stirring solution of alcohol **4** (1.56 g, 10.0 mmol) and pyridine (1.58 g, 20.0 mmol) in methylene chloride (20 mL) at 0 °C was added methylchloroformate over 5 min. The solution was allowed to reach room temperature overnight (12 h). The solution was washed with saturated aqueous ammonium chloride (3 × 10 mL), saturated aqueous sodium bicarbonate (3 × 10 mL), and saturated aqueous sodium chloride (3 × 10 mL). The organic layers were dried over sodium sulfate and concentrated in vacuo to give a light brown oil. Vacuum distillation at 120−125 °C at 0.01 mm gave the desired carbonate as a clear, colorless liquid (1.42 g, 68%). IR (neat): 3069, 2990, 2938, 1754, 1587, 1444, 1373, 1261, 1092, 1056 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.15 (d, J = 5.7 Hz, 1H), 5.92 (d, J = 5.5 Hz; 1H), 5.52 (br, s, 1H), 5.26 (d, J = 5.7 Hz, H), 4.64 (d, J = 5.7 Hz, 1H), 3.78 (s, 3H), 1.42 (s, 3H), 1.35 (s, 3H). ^{13}C NMR (75 MHz $CDCl_3$): δ 188.1, 138.5, 130.8,

112.3, 86.3, 84.0, 83.1, 54.9, 27.2, 25.6. HRMS: Calcd for $C_9H_{11}O_5$ ($M^+ - CH_3$): 199.0606. Found 199.0601.

(3*S*,4*R*,5*S*)-3-Phthalimido-4,5-*O*-isopropylidenedioxycyclopentene (3). A solution of carbonate **4a** and ***ent*-4a** (214.0 mg, 1.0 mmol), $Pd_2dba_3{\cdot}CHCl_3$ (26.0 mg, 0.025 mmol), and (*S*,*S*)-cyclohexyl ligand **10** (52.0 mg, 0.075 mmol) in methylene chloride (5.0 mL) at 0 °C under argon was stirred for 15 min. A solution of potassium phthalimide (204.3 mg, 1.1 mmol) and tetrahexylammonium bromide (478.1 mg, 1.1 mmol) was stirred in methylene chloride (5.0 mL) at 0 °C under argon for 15 min. This solution was added to the solution of ligand and the reaction stirred at 0 °C for 6 h. The reaction was allowed to warm to room temperature over 12 h and was then complete. Chromatography (1:5 ethyl acetate:hexane) gave the imide as a white solid (170.8 mg, 62%, ee 98%), mp 118−120 °C, $[\alpha]^{25}_D$ +287.6° (c = 1.15 DCM). Determination of enantiomer excess: HPLC (Chiracel OD column, 98:2 heptane/2-propanol, flow 0.7 mL/min, δ = 254) (−) enantiomer t_R = 11.40, (+) enantiomer t_R = 12.85 min. IR (KBr pellet): 3062, 2987, 1775, 1414, 1582, 1388, 1223, 1075, 1050 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.84−7.80 (m, 2H), 7.75−7.70 (m, 2H), 6.14 (dd, J = 5.6, 1.8 Hz, 1H), 5.65 (dd, J = 5.6, 2.3 Hz, 1H), 5.58 (d, J = 5.2 Hz, 1H), 5.33 (br s, 1H), 4.86 (d, J = 5.2 Hz, 1H), 1.47 (s, 3H), 1.36 (s, 3H). ^{13}C NMR (75 MHz $CDCl_3$): δ 169.3, 138.1 135.8, 133.5. 130.8, 124.9, 113.1, 87.3, 84.0, 62.2, 28.9, 27.2. HRMS: Calc′d for $C_{15}H_{12}NO_4$ ($M^+ - CH_3$): 270.0766. Found: 270.0768. Anal. Calcd for $C_{16}H_{15}NO_4$: C, 67.36, H, 5.30; N 4.91. Found: C 67.23, H 5.20, N 4.86.

(3*S*,4*R*,5*S*)-3-Amino-4,5-*O*-isopropyldenedioxycyclopentene. To a stirring solution of phthalimide **3** (85.6 mg, 0.3 mmol) in dry ethanol (3 mL) was added ethylenediamine (36.1 mg, 0.6 mmol). The solution was heated to reflux overnight (14 h) over which time a white precipitate had formed. To this mixture was added aqueous sodium hydroxide (0.5 M, 3 mL). The resulting solution was washed with methylene chloride (3 × 15 mL). The organic layers were dried over sodium sulfate and concentrated in vacuo to give the desired product as a clear, colorless oil (40.2 mg, 78%), $[\alpha]^{25}_D$ +148.6 (c = 0.35, MeOH) [lit.[1a] $[\alpha]^{25}_D$ + 148° (c = 0.39, MeOH). IR (neat): 3352, 3048, 2925, 1594, 1455, 1371, 1209, 1048 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.87−5.82 (m, 2H), 5.25 (d, J = 5.7 Hz, 1H), 4.34 (d, J = 5.7 Hz, 1H), 3.96 (d, J = 0.8 Hz, 1H), 1.39 (s, 3H), 1.32 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.3, 134.3, 112.5, 88.8, 86.2, 64.4, 28.8, 27.1.

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