Pergamon

Tetrahedron Letters 39 (1998) 7987–7990

TETRAHEDRON LETTERS

A Stereoselective and Efficient Route to (3S, 4R, 5S)-(+)-4,5-Dihydroxycyclopent-1-en-3-ylamine: the Side Chain of the Hypermodified Nucleoside Q

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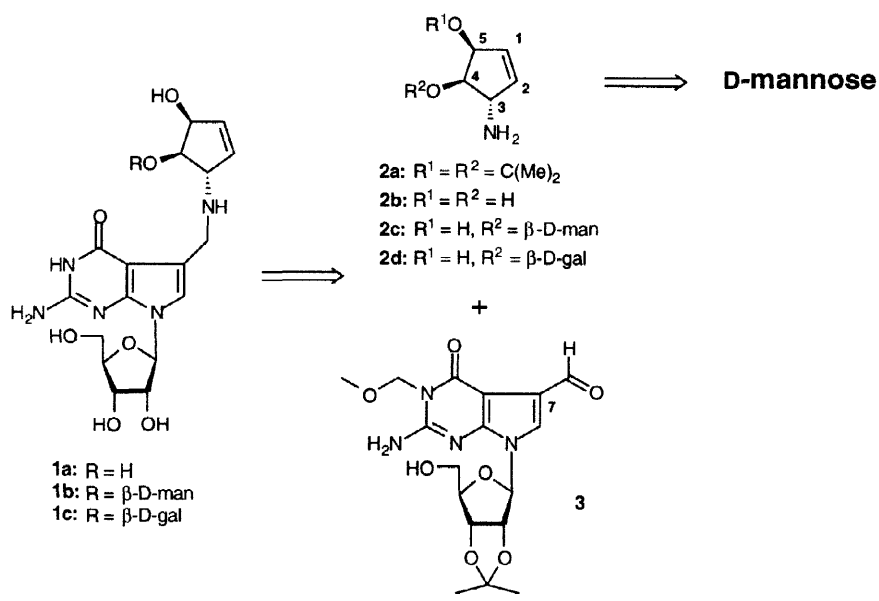
Received 9 July 1998; accepted 18 August 1998

Abstract: A stereoselective and high yielding route is described to a suitably protected derivative of (3S, 4R, 5S)-(+)-3-amino-4,5-dihydroxycyclopent-1-ene, the side chain moiety of queuosine. The synthetic route comprises a ring-closing metathesis (RCM) of a mannofuranose-derived diene followed by Overman rearrangement.

Key words: queuosine, ring-closing metathesis, Overman rearrangement, β-galactosylation

Thirty years ago, it was discovered[1] that the first position of the anticodon region of *Escherichia coli* $tRNA^{Tyr}$ is occupied by the nucleoside queuosine (so called nucleoside Q). Detailed structural analysis of this hypermodified nucleoside by Goto *et al.*[2] revealed that it consists of 7-deazaguanosine, the 7-position of which is connected, as in stucture **1a**, *via* a methylene bridge to the amino group of (3S, 4R, 5S)-(+)-4,5-dihydroxycyclopent-1-en-3-ylamine (**2b**) (Figure 1). Further studies showed that Q was not only present[3] in the same location of other *E coli* tRNA's (*i.e.* $tRNA^{His}$, $tRNA^{Asp}$, and $tRNA^{Asn}$), but also widely distributed[4] in tRNA's of plants and animals. Moreover, derivatives of Q in which the non-allylic hydroxyl group of the cyclopentenyl moiety of Q is β-glycosylated with either D-mannose (as in **1b**) or D-galactose (as in **1c**) have been isolated from rabbit liver.[5]

Figure 1

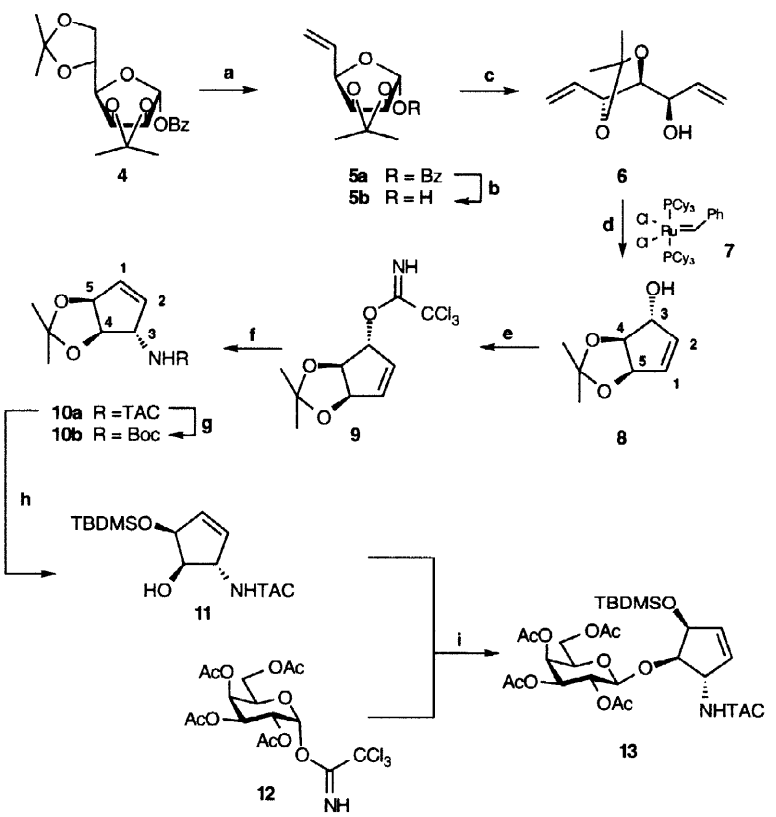


PII: S0040-4039(98)01738-9

One of the most promising routes of synthesis to Q thus far developed entails (see Figure 1) the highly efficient condensation[6] of the partially protected 7-deaza-guanosine derivative **3** with (+)-cyclopentenylamine acetonide **2a** followed by mild reduction of the *in situ* formed Schiff base. However, full implementation of this approach is hampered by the fact that an efficient route to a suitable dihydroxycyclopentenylamine building block is lacking. For example, a recently published route starting from (±)-dicyclopentadiene is a rather low yielding and time consuming process.[7a] With the objective to get a better insight into the biochemical and conformational properties of RNA fragments containing Q as well as its glycosylated derivatives, an efficient route to a dihydroxycyclopentenylamine building block would be highly desirable. We here report a convenient and stereoselective route to the properly protected building block (+)-**10a**.

The route of synthesis we followed to reach our goal is depicted in Scheme 1, and is based on an earlier reported[8] ring-closing metathesis (RCM) of a diene derived from readily available furanose sugars. Retrosynthetic analysis reveals that the synthesis of the target molecule **10a** (R= trichloroacetyl) can be achieved from the known[9] and easily accessible benzoyl-(2,3),(5,6)-di-*O*-isopropylidene-α-D-manno-furanose (**4**). Transformation of **4** into the requisite diene derivative **6** proceeded smoothly by following a well established sequence of reactions. Thus, regioselective removal of the 5,6-isopropylidene group in **4** followed by treatment of the crude diol derivative with triethylorthoformate led, after acid

Scheme 1



Reagents and conditions: **a**) 80% HOAc (aq), 40 °C, 4 h, then $HC(OEt_3)$, HOAc, 80 °C, 30 min, then Ph_3CCO_2H (0.45 mol%), neat, 170 °C, 5 h, 93% (three steps). **b**) KO*t*Bu, MeOH, 96%. **c**) $Ph_3P^+CH_3Br^-$, *n*BuLi, THF, -20 °C to RT, 16 h, 98%. **d**) **7** (0.5 mol%), CH_2Cl_2, 5 h, 95%. **e**) CCl_3CN, DBU, CH_2Cl_2, 0 °C, 10 min. **f**) xylenes, reflux, 4 h, 89% (2 steps). **g**) NaOH, EtOH, 70 °C, then Boc_2O, CH_2Cl_2, TEA, 70% (2 steps). **h**) HOAc (70% aq), 35 °C, overnight, then TBDMSCl (1.2 equiv.), pyridine, 35 °C, overnight, 70 % (two steps). **i**) **12** (2 equiv.), TMSOTf (0.01 equiv.), CH_2Cl_2, 0 °C, 10 min, 72%.

catalyzed thermal rearrangement[10] of the intermediate orthoester, to the isolation of **5a** in 93% yield over the three steps. Anomeric debenzoylation and consecutive Wittig olefination of **5b** gave, after purification by distillation, diene **6** as an oil in a yield of 87% based on **4**. RCM of **6** under the influence of Grubbs ruthenium catalyst **7**[11] (0.5 mol%) gave, after silica gel purification, the homogeneous cyclopentene derivative **8** in 95% yield.[12] 1,3-Transposition of the allylic alcohol in **8** to give the fully protected derivative **10a** could be readily effected via a [3,3] sigmatropic Overman rearrangement.[13] To this end, the allylic alcohol **8** was subjected to trichloroacetonitrile in the presence of DBU to afford crystalline imidate **9**[12] ($[\alpha]_D^{20}$ -121°, $CHCl_3$) in a near quantitative yield. Subsequent heating of the imidate in xylenes under reflux led to the isolation of fully protected **10a**[12] ($[\alpha]_D^{20}$ +130°, $CHCl_3$) as colourless needles in 89% yield. The observation that the direction of optical rotation is dextrarotatory for **10a**, and the opposite for **9**, is in complete agreement with Mill's rule extended by Brewster[14] for endocyclic olefins, indicating that the Overman rearrangement of (-)-**9** into (+)-**10a** is a stereoselective process. The (3S, 4R, 5S) stereochemistry of (+)-**10a** was also independently confirmed as follows. Deacylation of **10a** followed by treatment of **2a** (see Figure 1) with di-*t*-butyl dicarbonate gave the mono *N*-Boc-protected derivative (+)-**10b**, the specific optical rotation of which was in excellent agreement with the one reported earlier[7a] for the same compound. The usefulness of **10a** was illustrated further by its conversion into the β-(1→4)-galactosylated derivative **13**. Thus, removal of the acetonide function in **10a** with dilute acid followed by regioselective silylation of the allylic hydroxyl group with *t*-butyldimethylsilyl chloride gave the 5-O-TBDMS protected derivative **11**, as evidenced by NMR-spectroscopy, in 70% yield. Stereoselective galactosylation of **11** with the known[15] α-trichloroacetimidate **12** under the influence of a catalytic amount of trimethylsilyltriflate gave, after silica gel column chromatography, homogeneous **13**[12] in a yield of 72%.

The approach presented in this paper is in terms of stereochemistry, overall yield and ease of scaling up to multigram quantities of (+)-**10a** superior over the reported syntheses[7a,b] of the side chain of Q. Moreover, the now easily accessible derivative (+)-**10a** is an attractive asset in the preparation of Q (**2a**), its glycosylated (*i.e.* **1b**, **c**) and other derivatives[16] of Q according to the retrosynthetic scheme presented in Figure 1.

Acknowledgements: This work was financially supported by the Netherlands Foundation for Chemical Research (SON).

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(12) All compounds were fully characterised by ^{1}H-NMR, ^{13}C-NMR, MS and $[\alpha]_D$. Relevant examples: **8**; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.35 (s, 3H), 1.40 (s, 3H), 1.80 (bs, 1H), 4.53 (d, 1H, *J* 5.5 Hz), 4.80 (s, 1H), 5.30 (m, 1H), 5.92 (m, 1H), 6.03 (m, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 25.3, 26.8, 80.0, 83.9, 85.4, 111.2, 134.4, 134.6. MS (CI): *m/z* 157.2 $(M+H)^+$. **9**; ^{1}H-NMR (300 Mhz, $CDCl_3$): δ 1.38 (s, 3H), 1.45 (s, 3H), 4.70 (d, 1H, *J* 5.8 Hz), 5.33 (m, 1H), 5.76 (s, 1H), 6.04 (m, 1H), 6.22 (m, 1H), 8.48 (s, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 25.7, 27.2, 82.7, 83.9, 87.5, 91.0, 112.4, 130.6, 138.3, 161.9. IR (KBr): ν 3320, 1664 cm^{-1}. M.p. 91.5 °C. MS (CI): *m/z* 321.8 $(M+Na)^+$: 323.8 $(M+Na+2)^+$: 325.9 $(M+Na+4)^+$ 3:3:1. **10a**; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.36 (s, 3H), 1.44 (s, 3H), 4.57 (d, 1H, *J* 5.1 Hz), 4.84 (m, 1H), 5.33 (m, 1H), 6.15 (m, 1H), 6.58 (bd, 1H, *J* 6.1 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 25.6, 27.2, 63.0, 83.5, 84.3, 92.1, 111.6, 130.4, 136.7, 161.5. IR (KBr): ν 3380, 3320, 1685, 1515 cm^{-1}. M.p. 110.5 °C. MS (CI): *m/z* 321.8 $(M+Na)^+$: 323.8 $(M+Na+2)^+$: 325.9 $(M+Na+4)^+$ 3:3:1. **13**; ^{1}H-NMR (300 MHz, $CDCl_3$): 0.04 (s, 3H), 0.09 (s, 3H), 0.85 (s, 9H), 1.93 (s, 3H), 2.00 (s, 3H), 2.01 (s, 3H), 2.02 (s, 3H), 3.86 (t, 1H, *J* 6.5 Hz), 3.96 (t, 1H, *J* 5.5 Hz), 4.08 (m, 2H), 4.62 (dd, 1H, *J* 2.3 and 2.4 Hz), 4.70 (d, 1H, *J* 7.8 Hz), 4.93 (m, 2H), 5.16 (dd, 1H, *J* 2.6 and 7.8 Hz), 5.32 (d, 1H, *J* 3.2Hz), 5.77 (dd, 1H, *J* 1.7 and 4.4 Hz), 5.98 (m, 1H), 6.79 (d, 1H, *J* 8.5 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$): δ –5.1, –4.8, 18.2, 20.5, 20.6, 20.7, 25.7, 60.0, 61.1, 66.9, 68.8, 70.4, 71.0, 74.1, 83.1, 92.4, 100.9, 131.7, 136.0, 169.5, 170.0, 170.1, 170.3. MS (CI): m/z 728.2 $(M+Na)^+$: 730.2 $(M+Na+2)^+$: 732.2 $(M+Na+4)^+$ 3:3:1.

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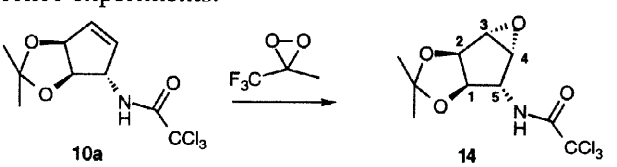
(16) *In situ* epoxidation of **10a** with 3-methyl-3-trifluoromethyldioxirane (*J. Org. Chem.* **1995**, *60*, 3887) afforded a single diastereoisomer of the crystalline epoxide **14** (m.p. 95 °C; 72% yield), as gauged by NOE difference experiments.



The same modification has been found (*J. Biol. Chem*, **1987**, *262*, 3462) in the side chain of Q from isoaccepting $tRNA^{Tyr}$ of *E. coli* MRE 600.