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

Huib Ovaa, Jeroen D. C. Codée, Bas Lastdrager, Herman S. Overkleeft, Gijsbert A. van der Marel and Jacques H. van Boom*

Leiden Institute of Chemistry, P. O. Box 9502, 2300 RA Leiden, The Netherlands 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. © 1998 Elsevier Science Ltd. All rights reserved.

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

Thirty years ago, it was discovered¹ 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 present³ in the same location of other *E coli* tRNA's (*i.e.* tRNA^{His}, tRNA^{Asp}, and tRNA^{Asn}), but also widely distributed⁴ 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



0040-4039/98/\$ - see front matter © 1998 Elsevier Science Ltd. All rights reserved. *Pll*: 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 condensation⁶ 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 (\pm)-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 reported⁸ 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 known⁹ 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



Reagents and conditions: a) 80% HOAc (aq), 40 °C, 4 h, then HC(OEt₃), HOAc, 80 °C, 30 min, then Ph₃CCO₂H (0.45 mol%), neat, 170 °C, 5 h, 93% (three steps). b) KOtBu, MeOH, 96%. c) Ph₃P*CH₃Br⁻, nBuLi, THF, -20 °C to RT, 16 h, 98%. d) 7 (0.5 mol%), CH₂Cl₂, 5 h, 95%. e) CCl₃CN, DBU, CH₂Cl₂, 0 °C, 10 min. f) xylenes, reflux, 4 h, 89% (2 steps). g) NaOH. EtOH, 70 °C, then Boc₂O, CH₂Cl₂, 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.), CH₂Cl₂, 0 °C, 10 min, 72%.

catalyzed thermal rearrangement¹⁰ of the intermediate orthoester, to the isolation of **5a** in 93% yield over the three steps. Anomeric debenzovlation 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 7¹¹ (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] signatropic 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} ($[\alpha]_{0}^{20}$ -121°, CHCl₃) in a near quantitative yield. Subsequent heating of the imidate in xylenes under reflux led to the isolation of fully protected $10a^{12}$ ($[\alpha]_{p}^{20}$ +130°, CHCl₃) 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 Brewster¹⁴ 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 \rightarrow 4)galactosylated derivative 13. Thus, removal of the acetonide function in 10a with dilute acid followed by regioselective silulation of the allulic hydroxyl group with t-butyldimethylsilul chloride gave the 5-O-TBDMS protected derivative 11, as evidenced by NMR-spectroscopy, in 70% yield. Stereoselective galactosylation of 11 with the known¹⁵ α -trichloroacetimidate 12 under the influence of a catalytic amount of trimethylsilyltriflate gave, after silica gel column chromatography, homogeneous 1312 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 derivatives¹⁶ of Q according to the retrosynthetic scheme presented in Figure 1.

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References and notes

- (1) Goodman, H. M.; Abelson, J.; Landy, A.; Brenner, S.; Smith, J. D. Nature 1968, 217, 1019.
- (2) Ohgi, T.; Kondo, T.; Goto, T. J. Am. Chem. Soc. 1979, 101, 3629.
- (3) Harada, F.; Nishimura, S. Biochemistry 1972, 11, 301.
- (4) Kasai, H.; Kuchino, Y.; Nihei, K.; Nishimura, S. Nucleic Acids Res. 1975, 2, 1931.
- (5) Kasai, H.; Nishimura, K.; MacFarlane, R. D.; Torgerson, D. F.; Ohashi, Z.; McCloskey, T. A.; Gross, H. J.; Nishimura, S. J. Am. Chem. Soc. 1976, 98, 5044.
- (6) Kondo, T.; Okamoto, K.; Ohgi, T.; Goto, T. Tetrahedron 1986, 42, 207.
- (7) (a) Tanaka, K.; Ogasawara, K. Synthesis 1996, 219. (b) Ohgi, T.; Goto, T. Tetrahedron Lett. 1976, 33, 367.
- (8) Ovaa, H.; Leeuwenburgh, M. A.; Overkleeft, H. S.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron Lett.* **1998**, *39*, 3025.
- (9) Ohrui, H.; Emoto, S. Tetrahedron Lett. 1975, 32, 2765.
- (10) Josan, J. S.; Eastwood, F. W. Jr. Carbohydr. Res. 1972, 24, 192.
- (11) Grubbs, R. H.; Chang, S. Tetrahedron 1998, 54, 4413.

- (12) All compounds were fully characterised by ¹H-NMR, ¹³C-NMR, MS and $[\alpha]_{D}$. Relevant examples: 8; ¹H-NMR (300 MHz, CDCl₃): 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). ¹³C-NMR (75 MHz, CDCl₃): 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; ¹H-NMR (300 Mhz, CDCl₃): 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). ¹³C-NMR (75 MHz, CDCl₃): δ 25.7, 27.2, 82.7, 83.9, 87.5, 91.0, 112.4, 130.6, 138.3, 161.9. IR (KBr): v 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; ¹H-NMR (300 MHz, CDCl₃): 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). ¹³C-NMR (75 MHz, CDCl₃): § 25.6, 27.2, 63.0, 83.5, 84.3, 92.1, 111.6, 130.4, 136.7, 161.5. IR (KBr): y 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; ¹H-NMR (300 MHz, CDCl₃): 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). ¹³C-NMR (75 MHz, CDCl₃): 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.
- (13) Overman, L. E. J. Am. Chem. Soc. 1976, 98, 2901.
- (14) Brewster, H. J. Am. Chem. Soc. 1959, 81, 5493.
- (15) Schmidt, R. R. Angew. Chem. Int. Ed. Engl. 1986, 25, 212.
- (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.