Llona-Minguez, S. and MacKay, S.P. (2014) Stereoselective synthesis of carbocyclic analogues of the nucleoside Q precursor (PreQ0). Beilstein Journal of Organic Chemistry, 10. pp. 1333-1338. ISSN 1860-5397, http://dx.doi.org/10.3762/bjoc.10.135

This version is available at https://strathprints.strath.ac.uk/53022/

Strathprints is designed to allow users to access the research output of the University of Strathclyde. Unless otherwise explicitly stated on the manuscript, Copyright © and Moral Rights for the papers on this site are retained by the individual authors and/or other copyright owners. Please check the manuscript for details of any other licences that may have been applied. You may not engage in further distribution of the material for any profitmaking activities or any commercial gain. You may freely distribute both the url (https://strathprints.strath.ac.uk/) and the content of this paper for research or private study, educational, or not-for-profit purposes without prior permission or charge.

Any correspondence concerning this service should be sent to the Strathprints administrator: strathprints@strath.ac.uk

The Strathprints institutional repository (https://strathprints.strath.ac.uk) is a digital archive of University of Strathclyde research outputs. It has been developed to disseminate open access research outputs, expose data about those outputs, and enable the management and persistent access to Strathclyde's intellectual output.
Stereoselective synthesis of carbocyclic analogues of the nucleoside Q precursor (PreQ₀)

Sabin Llona-Minguez*¹,² and Simon P. Mackay*¹

Abstract
A convergent and stereoselective synthesis of chiral cyclopentyl- and cyclohexylamine derivatives of nucleoside Q precursor (PreQ₀) has been accomplished. This synthetic route allows for an efficient preparation of 4-substituted analogues with interesting three-dimensional character, including chiral cyclopentane-1,2-diol and -1,2,3-triol derivatives. This unusual substitution pattern provides a useful starting point for the discovery of novel bioactive molecules.

Introduction
7-Deazapurine (pyrrolo[2,3-d]pyrimidine) nucleosides are commonly found in nature playing a variety of roles such as building blocks of nucleic acids and tRNA, metabolites or antimetabolites [1]. Deazapurine ribonucleosides also show interesting pharmacological profiles including antibacterial, antiviral and anticancer properties [2-4]. Nucleoside Q precursor (PreQ₀) 1 is a common precursor in the biosynthesis of queuosine (Q, 2) and archaeosine (G⁺, 3), two hyper-modified nucleosides present in the tRNA of prokaryote/eukaryote and euryarchaeota, respectively [5,6]. In turn, the biosynthesis of PreQ₀ originates from guanosine 5’-triphosphate (GTP, 4) [7] (Figure 1) and involves four steps via a tetrahydropterine intermediate.

The pyrrolo[2,3-d]pyrimidine core is a privileged scaffold for the development of kinase inhibitors; an inspection of the medicinal chemistry literature reveals >200 publications in the field. Additionally, PreQ₀ meets all the criteria dictated by the “2-0” rule of kinase-likeness proposed by Aronov et al. [8]. It is likely that compounds derived from PreQ₀ display kinase activity.
7-Deazapurine nucleoside chemistry has been the subject of extensive study [1] and several syntheses of the PreQ\textsubscript{0} base or ribonucleoside [9-16] and queuosine [17] have been reported in the literature. Despite this long-lasting interest, examples of purine-based nucleosides containing a sugar or carboxylic motif at the 4-position of the heterocyclic core (systematic numbering) are scarce in the chemical literature and the methods available generally lack experimental information, making them unsatisfactory [18-25]. Inspired by the cyclopentane-1,2,3-triol motif present in noraristeromycin 5 (Figure 2), an IsB kinase inhibitor with antiviral and anti-inflammatory activity [26,27], we decided to investigate a synthetic route that would allow for the incorporation of carbocyclic systems with interesting three-dimensional character at the 4-position of PreQ\textsubscript{0} as part of our fragment-based kinase inhibitor library generation programme.

**Results and Discussion**

Our retrosynthetic approach introduces the diversity point at a late stage and takes advantage of the heterocyclic lactam present in PreQ\textsubscript{0} after activation and subsequent nucleophilic aromatic substitution. This convergent synthesis allowed us to prepare diverse chiral amine building blocks and react them with a common halo-purine intermediate to obtain the desired final products. The pyrrolo[2,3-d]pyrimidine core of PreQ\textsubscript{0} was furnished following a method described by Klepper et al. [13] (Figure 3). The two step process started with the formylation of chloroacetonitrile with methyl formate. The resulting volatile

![Figure 1: Biosynthetic pathway leading to nucleosides queuosine and archeosine.](image1)

![Figure 2: Chemical structure of noraristeromycin.](image2)

![Figure 3: Synthesis of PreQ$\textsubscript{0}$ and chloro-intermediate 9.](image3)
and unstable chloroaldehyde 6 was used without further purification. Cyclocondensation of 6 with 2,4-diamino-4-hydroxy-pyrimidine afforded 1 regiospecifically with no detectable formation of the undesired 6-substituted-furo[2,3-\textit{d}]pyrimidine 7. Direct chlorination of 1 in a moderate scale (1 g) using POCl$_3$ proved to be very low yielding [28]. It remains unclear if this was due to the poor solubility of PreQ$_0$ or to the presence of unprotected amino functionalities. In order to overcome this issue, the exocyclic amine was protected [14] (Figure 3). The resulting pivalamide 8 proved to be more soluble than 1 and the subsequent halogenation step was accomplished in the presence of a phase transfer catalyst, affording the desired chloro-intermediate 9 in fair yield. In our hands, nucleophilic aromatic substitution on 9 using amines of diverse nature usually proceeds smoothly and allows for a clean pivalamide deprotection [29]. For this reason we decided to couple the chiral amines of interest and remove protecting groups in a one-pot procedure.

First we investigated a more synthetically accessible (1RS,2SR,3RS)-3-aminoepentane-1,2-diol core. Our previous experience in coupling diols and triols at high temperatures with chloro-intermediate 9 showed that more than one unprotected alcohol functionality leads to complex reaction mixtures and very low yields of isolated products [29], hence we protected all hydroxy groups as esters. We chose the benzoate protecting group to generate UV–visible intermediates and because its ease of cleavage under basic conditions is extremely sensitive to the presence of moisture and oxygen. The reaction proceeded smoothly and the 1H NMR spectra of the crude reaction mixture showed a 96:4 ratio of cis- to trans-isomers. After column chromatography the isolated diol 12 showed a diastereomeric purity of >99% by 1H NMR. The dibenzoate 13 was obtained in good yield following standard acylation conditions [31]. Final removal of the two benzyl groups was accomplished in excellent yield using catalytic hydrogenation [30], using EtOAc as a co-solvent to improve the substrate solubility. Amine 14 was coupled with 9 and the pivalamide and benzoate groups were cleaved in the one-pot procedure previously described to afford 15, the (1RS,2SR,3RS)-3-aminoepentane-1,2-diol derivative of PreQ$_0$.

Adapting a protocol developed by Springthorpe et al. [32], we then investigated a route to prepare the enantiopure (1S,2R,3S,4R)-4-aminoepentane-1,2,3-triol analogue of PreQ$_0$ 16 (Figure 5). The first step is a Tsuji–Trost alkylation of sodium di-\textit{tert}-butyliminodicarboxylate. The reaction proceeded with an overall retention of configuration as expected and the 1H NMR spectra of the crude reaction mixture only showed the desired diastereomer 17. Several known catalytic systems were tested [29]: Pd(PPh$_3$)$_4$/PPh$_3$ in THF/DMF [33], Pd$_2$(dba)$_3$/diphos in THF/DMF [34], Pd$_2$(dba)$_3$/dppf in THF [35]. The first set of conditions proved to be the most successful, although addition of DMF was required to improve the solubility of the reactants. It is worth noting that this reaction proved to be extremely sensitive to the presence of moisture and oxygen. The bulky nature of the nucleophile used aided in the diastereoselectivity of the following syn-dihydroxylation. Using the Upjohn conditions previously described we obtained the desired

![Figure 4: Synthesis of 15, a (1RS,2SR,3RS)-3-aminoepentane-1,2-diol derivative of PreQ$_0$. Reagents and conditions: (a) NBS, (PhCO$_2$)$_2$, CCl$_4$, 1 h, 90 °C; (b) NH(Bn)$_2$, CCl$_4$, 12 h, rt, 70% (over two steps); (c) OsO$_4$, NMO, acetone/H$_2$O, 4 h, rt, 72%, 96% ds; (d) BzCl, pyr, 24 h, 0 °C to rt, 84%; (e) H$_2$ (1 atm), Pd(OH)$_2$, EtOH/EtOAc, 16 h, rt, 98%; (f) 9, Et$_3$N, n-BuOH, 16 h, 130 °C; (g) KOH, n-BuOH/EtOH, 16 h, 80 °C, 42%.](image-url)
1336

Figure 5: Synthesis of 16, a (1R,2R,3S,4R)-4-aminocyclopentane-1,2,3-triol derivative of PreQ<sub>0</sub>. Reagents and conditions: (a) Pd(PPh<sub>3</sub>)<sub>4</sub>, PPh<sub>3</sub>, NaH, NH(Boc)<sub>2</sub>, THF/DMF, 1 day, 50 °C, 42%; (b) OsO<sub>4</sub>, NMO, acetone/H<sub>2</sub>O, 1 day, rt, 83%; (c) BzCl, pyr, 17 h, 0 °C to rt, 74%; (d) 4 M HCl in 1,4-dioxane, 16 h, 0 °C to rt, 76%; (e) 9, Et<sub>3</sub>N, n-BuOH, 16 h, 130 °C; (f) KOH, n-BuOH/EtOH, 16 h, 80 °C, 33%.

triol 18 in good yield and excellent diastereoselectivity (>99% by <sup>1</sup>H NMR after column chromatography) [30]. Tri-benzoate 19 was subsequently obtained in good yield using the standard benzoylation conditions [31]. Final removal of the two BOC protecting groups using 4 M HCl in 1,4-dioxane yielded amine 20 as the hydrochloride salt. Amine 20 was coupled with chloro-intermediate 9 and the remaining four protecting groups were cleaved in a one-pot procedure under basic conditions, generating the desired triol 16.

To extend into hydrophobic chemical space around our PreQ<sub>0</sub> analogues, we prepared two novel derivatives containing the unusual 3-arylcyclohexylamine chiral motif present in 21 and 22. Zhou et al. had reported an asymmetric synthesis leading to the cis-3-arylcyclohexanamines with reasonable diastereoselectivity [36], but since initially we did not require an enantioselective synthesis and the Zhou method employed rather expensive reagents, we investigated a simpler and cheaper route to access both cis- and trans-isomers. We envisioned a stereoselective synthesis that would potentially allow for the introduction of diverse aryl groups at the 3-position of the cyclohexane ring using commercially available arylboronic acids as building blocks, and Pd catalysis to form the new C–C bond, followed by a highly diastereoselective ketone-to-amine conversion. Others have reported on similar preparations of 3-phenylcyclohexanamines, although with poor diastereomeric control [37,38]. 1-Cyclohex-2-enone provided the two required synthetic handles: a sp<sup>2</sup> carbon for Pd chemistry and a ketone for further derivatization into an amine group (Figure 6). The synthesis of cis- and trans-3-arylcyclohexamelines 23 and 24 started with a Pd<sup>II</sup>-catalyzed Miyaura 1,4-conjugate addition of phenylboronic acid to cyclohexenone [39]. The resulting ketone 25 was reduced to the axial [40,41] and equatorial [40] alcohols 26 and 27 with excellent diastereoselectivity thanks to steric control of the hydride source. After column chromatography both alcohols showed a diastereomeric purity of >99% by <sup>1</sup>H NMR. Mitsunobu reaction on the secondary alcohols using DEAD or DIAD did not provide the desired azides [42,43] nor did a one-pot Appel reaction/nucleophilic substitution/Staudinger reaction protocol involving a double inversion of configuration [44]. Mesylation of 26 and 27 lead to intermediates 28 and 29 [45], which were subsequently reacted with sodium azide inverting the stereochemistry as required [46]. A final transfer hydrogenation of 30 and 31 yielded the desired amines rapidly and with excellent yields [47]. Amines 23 and 24 were reacted with chloro-intermediate 9 and the pivalamide groups were cleaved under basic hydrolysis conditions to yield 21 and 22.

**Conclusion**

In conclusion, a concise and stereoselective synthesis of novel cyclopentyl and cyclohexyl analogues of PreQ<sub>0</sub> has been developed to expand our fragment-based kinase library. This synthetic protocol involves asymmetric syntheses of hydroxyl-protected (1RS,2SR,3RS)-3-aminocyclopentan-1,2-diol and (1S,2R,3S,4R)-4-aminocyclopentan-1,2,3-triol or cis- and trans-3-arylcyclohexlamines, which are in turn reacted with a conveniently PreQ<sub>0</sub>-derived halo-intermediate and subsequently deprotected in a one-pot fashion. Pharmacological assessment of these novel PreQ<sub>0</sub> derivatives is currently underway in a variety of kinase-inhibitory studies and will be reported in due course.
Figure 6: Synthesis of 21 and 22, 3-arylcyclohexylamine derivatives of PreQ₀. Reagents and conditions: (a) PhB(OH)₂, Pd(OAc)₂, bpy, H₂O/THF/AcOH, 3 days, 80 °C, 98%; (b) K-Selectride, THF, 2 h, −90 °C; then KOH (aq), H₂O₂, 30 min, rt, 80%, 99% ds; (c) LiAlH₄, Et₂O, 1.5 h, 0 °C to rt; then NaOH (aq), 30 min, rt, 76%, 97% ds (d) MsCl, Et₃N, THF, 16 h, rt, (trans 67%, cis 64%); (d) NaN₃, DMF, 2 days, 80 °C, (trans 56%, cis 67%); (f) HCO₂NH₄, Pd/C, MeOH, 1.5 h, reflux, (trans 92%, cis 94%); (g) 9, Et₃N, n-BuOH, 16 h, 130 °C; (h) KOH, n-BuOH/EtOH, 16 h, 80 °C, (trans 38%, cis 50%).

Supporting Information
Supporting Information File 1
General methods, experimental procedures and copies of ¹H/¹³C NMR spectra and HPLC UV traces of final compounds 15, 16, 21 and 22. [http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-10-135-S1.pdf]

Acknowledgements
The authors would like to thank Stuart Lang for insightful comments and manuscript reviewing. S. Llona-Minguez and S. P. Mackay have received funding from the University of Strathclyde studentship scheme and Cancer Research UK to pursue inhibitory IκB kinase inhibitors and a patent application is in preparation.

References
1. Seela, F.; Peng, X. Curr. Top. Med. Chem. 2006, 6, 867–892. doi:10.2174/156802606777303649
2. Suhaladnlik, R. J. Pyrrolopyrimidine Nucleosides. "Nucleoside Antibiotics"; Wiley-Interscience: New York, 1970.
3. Ritch, P. S.; Glazer, R. I. Pyrrolo[2,3-d]pyrimidine nucleosides. Developments in Cancer Chemotherapy; CRC Press: Florida, 1984.
4. Martin, J. C. Nucleotide Analogues as Antiviral Agents; American Chemical Society: Washington, 1989. doi:10.1021/bk-1989-0401
5. Morris, R. C.; Elliott, M. S. Mol. Genet. Metab. 2001, 74, 147–159. doi:10.1006/mgme.2001.3216
6. Phillips, G.; Swairjo, M. A.; Gaston, K. W.; Bailly, M.; Limbach, P. A.; Iwata-Reuyl, D.; de Crécy-Lagard, V. ACS Chem. Biol. 2011, 7, 300–305. doi:10.1021/cb200361w
7. McCarty, R. M.; Sornogyl, A.; Lin, G.; Jacobsen, N. E.; Bandarian, V. Biochemistry 2009, 48, 3847–3852. doi:10.1021/bi900400e
8. Aronov, A. M.; McClain, B.; Moody, C. S.; Murcko, M. A. J. Med. Chem. 2008, 51, 1214–1222. doi:10.1021/jm700361b
9. Cheng, C. S.; Hinshaw, B. C.; Panzica, R. P.; Townsend, L. B. J. Am. Chem. Soc. 1976, 98, 7870–7872. doi:10.1021/ja00440a094
10. Kondo, T.; Okamoto, K.; Ohgi, T.; Goto, T. Tetrahedron 1986, 42, 207–213. doi:10.1016/S0040-4020(01)87419-6
11. Migawa, M. T.; Hinkle, J. M.; Hoops, G. C.; Townsend, L. B. Synth. Commun. 1996, 26, 3317–3322. doi:10.1080/00397919608004641
12. Ramzaeva, N.; Becher, G.; Seela, F. Synthesis 1998, 1327–1330. doi:10.1055/s-1998-6088
13. Klepper, F.; Polborn, K.; Carell, T. Helv. Chim. Acta 2005, 88, 2610–2616. doi:10.1002/hic.200509201
14. Brückl, T.; Klepper, F.; Gutamied, K.; Carell, T. Org. Biomol. Chem. 2007, 5, 3821–3825. doi:10.1039/b713309j
15. Brückl, T.; Thom, A. J.; Wagner, A. J.; Knochel, P.; Carell, T. Eur. J. Org. Chem. 2010, 6517–6519. doi:10.1002/ejoc.201000987
16. Ming, X.; Seela, F. Chem. Biodiversity 2010, 7, 2616–2621. doi:10.1002/cbdv.201000239
17. Klepper, F.; Jahn, E.-M.; Hinkmann, V.; Carell, T. Angew. Chem., Int. Ed. 2007, 46, 2325–2327. doi:10.1002/anie.200604579
18. Arndt, D.; Graff, A. Z. Chem. 1977, 17, 224–225.
19. Anderson, B. G.; Bauta, W. E.; Cantrell, W. R., Jr.; Engles, T.; Lovett, D. Org. Process Res. Dev. 2008, 12, 1229–1237. doi:10.1021/op080182x
20. Arndt, D.; Graff, A. S-Glycosides of arabinofuranose. German Democratic Republic Patent DD107278A1, 1974.
21. Claiborne, C. F.; Critchley, S.; Langston, S. P.; Ohlava, E. J.; Peluso, S.; Weatherhead, G. S.; Vyskocil, S.; Visiers, I.; Mizutani, H.; Cullis, C. Preparation of carbocyclic purine nucleoside analogs as antitumor agents and inhibitors of E1 activating enzymes. WO Patent WO2008019124A1, Feb 14, 2008.

22. Fujishima, T.; Uchida, K.; Yoshino, H. N6-(β-D-Ribofuranosyl)adenine. Japanese Patent JP50034040B, 1975.

23. Lüipke, U.; Seela, F.

24. Jain, P. C.; Anand, N.

25. Goodman, I.; Salce, L.; Hitchings, G. H. J. Med. Chem. 1968, 11, 516–521. doi:10.1021/jm00309a024

26. Llona-Minguez, S.; Baigel, J.; Mackay, S. P. Pharm. Pat. Anal. 2013, 2, 481–498. doi:10.4155/ppa.13.31

27. Ito, M.; Hamano, T.; Komatsu, T.; Asamitsu, K.; Yamakawa, T.; Okamoto, T. Mod. Rheumatol. 2014. doi:10.3109/14397595.2013.879416

28. Gibson, C. L.; La Rosa, S.; Ohta, K.; Boyle, P. H.; Leurquin, F.; Lemaçon, A.; Suckling, C. J. Tetrahedron 2004, 60, 943–959. doi:10.1016/j.tet.2003.11.030

29. Unpublished results.

30. Bond, C. W.; Cresswell, A. J.; Davies, S. G.; Fletcher, A. M.; Humphries, R. G.; Hunt, S. F.; Ince, F.; Ingall, A. H.; Kirk, I. P.; Martin, B. P.; McGinnity, D. F.; Mortimore, M. P.; Paine, S. W.; Pairaudeau, G.; Patel, A.; Rigby, A. J.; Riley, R. J.; Teobald, B. J.; Tomlinson, W.; Webborn, P. J. H.; Willis, P. A. Bioorg. Med. Chem. Lett. 2007, 17, 6013–6018. doi:10.1016/j.bmcl.2007.07.057

31. Li, J.; Lowary, T. L. Org. Lett. 2008, 10, 881–884. doi:10.1021/ol070341y

32. Springthorpe, B.; Bailey, A.; Barton, P.; Birkinshaw, T. N.; Bonnett, R. V.; Brown, R. C.; Chapman, D.; Dixon, J.; Guille, S. D.; Humphries, R. G.; Hunt, S. F.; Ince, F.; Ingall, A. H.; Kirk, I. P.; Leeson, P. D.; Leff, P.; Lewis, R. J.; Martin, B. P.; McGinnity, D. F.; Mortimore, M. P.; Paine, S. W.; Pairaudeau, G.; Patel, A.; Rigby, A. J.; Riley, R. J.; Teobald, B. J.; Tomlinson, W.; Webborn, P. J. H.; Willis, P. A. Bioorg. Med. Chem. Lett. 2007, 17, 6013–6018. doi:10.1016/j.bmcl.2007.07.057

33. Deardorff, D. R.; Linde, R. G.; II; Martin, A. M.; Shulman, M. J. Org. Chem. 1999, 54, 2759–2762. doi:10.1021/jo00272a059

34. Connell, R. D.; Rein, T.; Aakermark, B.; Helquist, P. J. Org. Chem. 1988, 53, 3845–3849. doi:10.1021/jo00251a035

35. Dauvergne, J.; Happe, A. M.; Jadhav, V.; Justice, D.; Matos, M.-C.; McCormack, P. J.; Pitts, M. R.; Roberts, S. M.; Singh, S. K.; Snape, T. J.; Whittall, J. Tetrahedron 2004, 60, 2559–2567. doi:10.1016/j.tet.2004.01.046

36. Zhou, J.; List, B. J. Am. Chem. Soc. 2007, 129, 7498–7499. doi:10.1021/ja072134j

37. Kajita, T.; Matsumoto, T. Process for the preparation of optically active trans-cyclohexylamine compounds. WO Patent WO2000000459A1, Jan 6, 2000.

38. Gomtsyan, A.; Daanen, J. F.; Gfesser, G. A.; Kort, M. E.; Lee, C.-H.; McDonald, H. A.; Putfarochen, P. S.; Voight, E. A.; Kym, P. R. Preparation of urea compounds TRPV1 antagonists for treating pain. U.S. Patent US20120245163A1, Sept 27, 2012.

39. Lu, X.; Lin, S. J. Org. Chem. 2005, 70, 9651–9653. doi:10.1021/jo051561h

40. Cieplak, A. S. J. Am. Chem. Soc. 1981, 103, 4540–4552. doi:10.1021/ja00405a041

41. Brown, H. C.; Krishnamurthy, S. J. Am. Chem. Soc. 1972, 94, 7159–7161. doi:10.1021/ja00775a053

42. Scott, J. P.; Alam, M.; Bremer, N.; Goodyear, A.; Lam, T.; Wilson, R. D.; Zhou, G. Org. Process Res. Dev. 2011, 15, 1116–1123. doi:10.1021/op200000u

43. Aicher, T. D.; Chicarelli, M. J.; Hinkel, R. J.; Tian, H.; Wallace, O. B.; Chen, Z.; Mabry, T. E.; McCowan, J. R.; Snyder, N. J.; Winneroski, L. L., Jr.; Allen, J. G. Preparation of cycloalkyl lactam derivatives, particularly N-substituted pyrrolidin-2-ones, as inhibitors of 11-beta-hydroxysteroid dehydrogenase 1. WO Patent WO2006049952A1, May 11, 2006.

44. Sagar Reddy, G. V.; Rao, G. V.; Subramanayam, R. V. K.; Iyengar, D. S. Synth. Commun. 2000, 30, 2233–2237. doi:10.1080/003979100080807402

45. Zhang, Q.; Ma, X.; Ward, A.; Hong, W.-X.; Jaaokla, V.-P.; Stevens, R. C.; Finn, M. G.; Chang, G. Angew. Chem., Int. Ed. 2007, 46, 7023–7025. doi:10.1002/anie.200701556

46. Lednicer, D.; Emmert, D. E.; Lahti, R.; Rudzik, A. D. J. Med. Chem. 1972, 15, 1239–1243. doi:10.1021/ja00282a009

47. Paryzek, Z.; Koenig, H.; Tabaczka, B. Synthesis 2003, 2023–2026. doi:10.1055/s-2003-41024

License and Terms
This is an Open Access article under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

The license is subject to the Beilstein Journal of Organic Chemistry terms and conditions: (http://www.beilstein-journals.org/bjoe)

The definitive version of this article is the electronic one which can be found at: doi:10.3762/bjoc.2014.1513.