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Chiral base route to functionalised cyclopentenyl amines: formal synthesis of the cyclopentene core of nucleoside Q

Sally J. Oxenford,[a] Peter O'Brien[a,*] and Mark R. Shipton[b]

[a]*Department of Chemistry, University of York, Heslington, York YO10 5DD, UK*
[b]*GlaxoSmithKline, Medicines Research Centre, Gunnels Wood Road, Stevenage SG1 2NY, UK*

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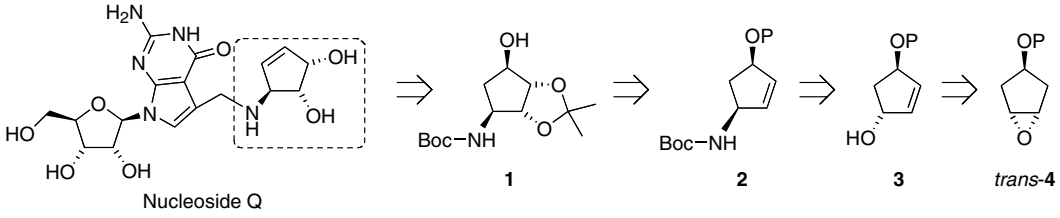
Abstract—A chiral base route to a range of highly functionalised amino cyclopentenes has been developed. The key asymmetric step involved the chiral lithium amide base-mediated rearrangement of a protected *trans*-4-hydroxy cyclopentene oxide to give an allylic alcohol (88% ee). Subsequent Overman rearrangement gave a protected *trans*-1,2-aminocyclopentenol whereas Mitsunobu substitution with BocNHNs gave a protected *cis*-amino cyclopentenol. Both are proven intermediates for natural product synthesis. The protected *cis*-aminocyclopentenol was transformed in a few steps into a precursor of the cyclopentene core of nucleoside Q, a natural product whose deficiency in animals is related to tumour growth.

Our group has an ongoing interest in the use of chiral base methodology for the synthesis of cyclic allylic amines.[1–4] Recently, we turned our attention to developing a chiral base route to the cyclopentene fragment of nucleoside Q.[5] Nucleoside Q, also known as queuosine, is widely distributed in tRNAs of plants and animals[6] and is of current interest since deficiency of nucleoside Q is related to tumour growth.[7] Recent synthetic work[8–11] has culminated in two enantioselective syntheses of the cyclopentene core, independently developed by Kim and Miller[10] and Trost and Sorum.[11] The penultimate compound in Miller's route was amino alcohol **1**[12] which was mesylated and eliminated using a dilute solution of DBU to give an allylic amine suitable for nucleoside Q synthesis.[10] Racemic **1** and its Boc-deprotected version have also been utilised in routes to antiviral carbocyclic nucleoside analogues[13,14] and the antitumour compound neoplanacin A.[15]

Our proposed route to the key intermediate, amino alcohol **1**, is outlined below. Amino alcohol **1** would be derived from amino cyclopentenol **2**,[16] itself obtained by a Mitsunobu reaction on allylic alcohol **3** using an appropriate nitrogen source. The chiral base-mediated rearrangement of epoxide *trans*-**4** would be used to produce the required allylic alcohol **3**. Although much is known on the rearrangement of the corresponding *cis*-cyclopentene oxides,[17,18] we were surprised to find that the best enantioselectivity for rearrangement of epoxide *trans*-**4** (P = TBS) was only 73% ee.[18e,f] This observation encouraged us to implement this particular chiral base strategy for the synthesis of amino alcohol **1**.



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* Corresponding author. Tel.: +44 01904 432535; fax: +44 01904 432516; e-mail: paob1@york.ac.uk

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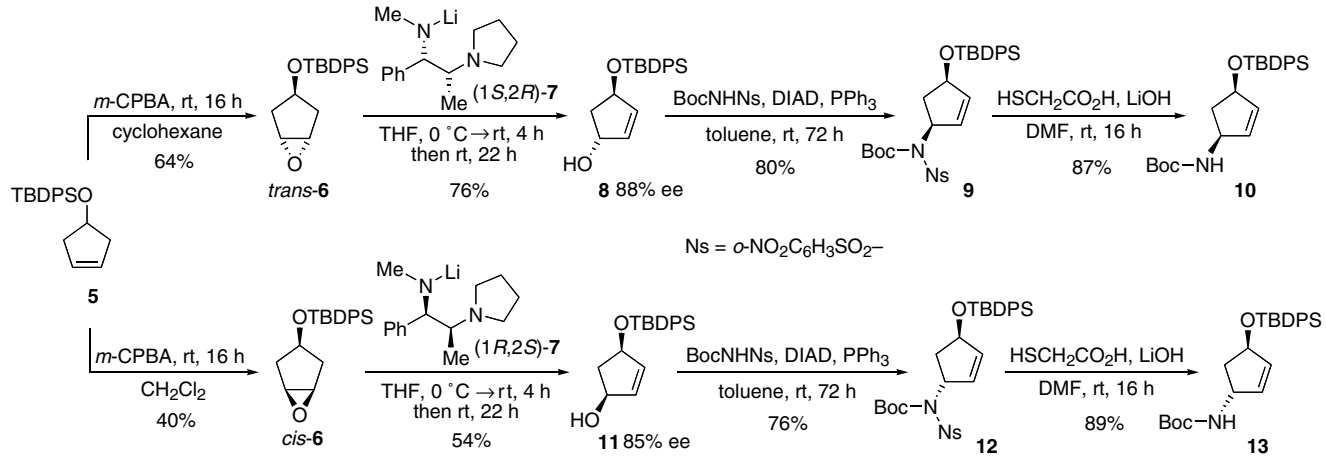
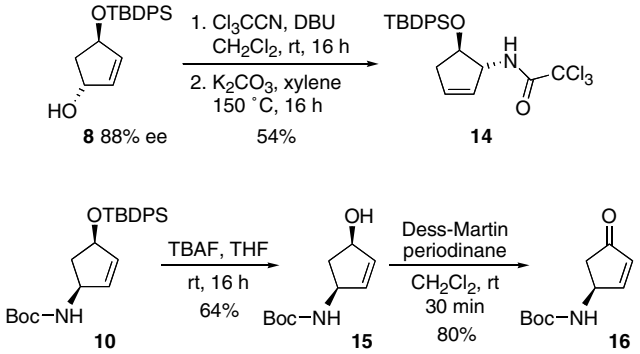


Furthermore, we also developed syntheses of a range of functionalised amino cyclopentenes that have been successfully employed in a range of synthetic endeavours by other groups (vide infra). Herein we describe our results.

To start with, commercially available 3-cyclopenten-1-ol[19] was TBDPS-protected and epoxidised using *m*-CPBA in cyclohexane to give a good (64%) isolated yield of epoxide *trans*-**6**. The *trans*-selectivity was much lower in dichloromethane but this produced the highest isolated yield of the diastereomeric epoxide *cis*-**6** (40%).[18f,20] Next, the key chiral base-mediated rearrangements were investigated. After a screen of alcohol protecting group and chiral base structure, we found that rearrangement of the TBDPS-protected epoxides *trans*- and *cis*-**6** using our[21] norephedrine-derived chiral bases (1*S*,2*R*)-**7** and (1*R*,2*S*)-**7** were optimal in terms of yield and enantioselectivity. Reaction of epoxide *trans*-**6** using (1*S*,2*R*)-**7** gave allylic alcohol **8** {$[\alpha]_D$ +56.7 (*c* 1.0, $CHCl_3$)} in 76% yield and 88% ee (by Mosher's ester formation). Significantly, this is a 15% ee improvement on the highest previously reported enantioselectivity for rearrangement of a protected *trans*-4-hydroxycyclopentene oxide.[18e,f] Under similar conditions, epoxide *cis*-**6** was rearranged using (1*R*,2*S*)-**7** to give allylic alcohol **11** {$[\alpha]_D$ +22.0 (*c* 1.0, $CHCl_3$)} in 54% yield and 85% ee. Similarly high enantioselectivity for the rearrangement of other protected *cis*-4-hydroxycyclopentene oxides has been reported by other groups.[18c–f]

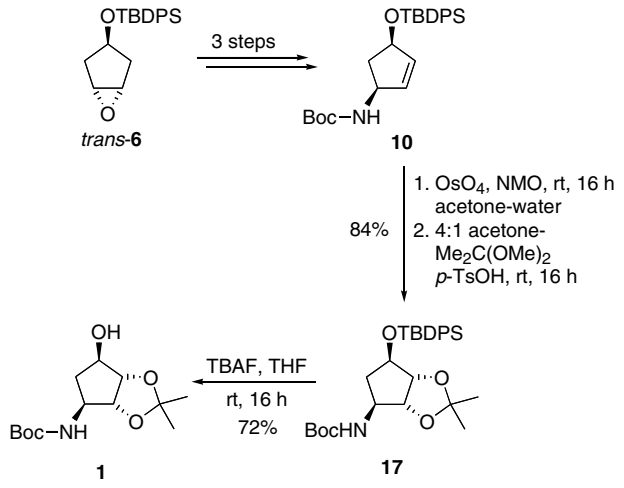
Although allylic alcohol **8** was of more interest due to our proposed nucleoside Q synthesis, we converted both allylic alcohols **8** and **11** into their corresponding amino ethers. For this, a Mitsunobu protocol using BocNHNs (Ns = *o*-$NO_2C_6H_3SO_2$–), independently developed by ourselves[4,22] and Fukuyama and co-workers,[23] was used. Thus, reaction of allylic alcohol **8** with BocNHNs/PPh_3/DIAD gave amino ether **9** which was smoothly deprotected using mercaptoacetic acid to give partially deprotected amino ether **10**, suitable for nucleoside Q synthesis. In the same way, allylic alcohol **11** gave amino ether **12** and thence NHBoc amino ether **13**. Each of **8**–**13** are useful synthetic building blocks. As examples, Ogasawara and co-workers used a differently protected version of *ent*-**10** in a concise route to (-)-kainic acid;[24] Trost et al. prepared a carbovir precursor from a benzoate ester of *ent*-**10**;[16f] Miller and co-workers described the conversion of an acetate ester of *ent*-**10** into (+)-uracilpolyoxin C[25] and Schaudt and Blechert converted the *N*-allylated amino alcohol of **13** into (+)-astrophylline.[16b] Our route to these key intermediates is notable since either enantiomer of **8**–**13** can be obtained simply by using the appropriate enantiomer of chiral base **7** and epoxide *trans*- or *cis*-**6**.

Further transformations into other useful compounds were also explored. Thus, Overman rearrangement[26] of allylic alcohol **8** gave a 54% yield of allylic amide **14**, analogous to a compound used by Johnson and co-workers in the synthesis of natural 3-hydroxyproline.[27] Alternatively, deprotection of amino ether **10** using TBAF gave amino alcohol **15** {$[\alpha]_D$ −56.3 (*c* 1.0, $CHCl_3$), 88% ee} of known absolute stereochemistry {$[\alpha]_D$ −69.0 (*c* 1.0, $CHCl_3$) for **15** of 98% ee[28]} thus confirming the stereochemical assignments in this series of compounds. Dess–Martin periodinane oxidation of **15** then generated amino ketone **16** {$[\alpha]_D$ −51.1 (*c* 1.0 in $CHCl_3$) (lit.,[16a] $[\alpha]_D$ +69.6 (*c* 2.6 in $CHCl_3$) for *ent*-**16** of >99% ee)} which has recently been used by Lee and Miller to prepare 4-acylamino analogues of LY354740[28] and by Roberts and co-workers for the synthesis of some novel prostaglandin analogues.[29]



With a range of synthetically useful compounds prepared, we then completed our planned synthesis of Miller's nucleoside Q intermediate, amino alcohol **1**. Thus, amino ether **10** (easily prepared in five steps from commercially available 3-cyclopenten-1-ol[19]) was subjected

to standard Upjohn dihydroxylation followed by acetonide formation. In this way, acetonide **17** was obtained as a single diastereomer in 84% yield over the two steps. The steric bulk and the *cis* arrangement of the NHBoc and silyl ether groups in **10** ensured a highly diastereoselective dihydroxylation process.[30] Finally, TBAF deprotection of the silyl ether in **17** produced amino alcohol **1** of 88% ee, $[\alpha]_D$ −18.6 (*c* 1.0 in CH_2Cl_2) {lit.,[12] $[\alpha]_D$ −20.2 (*c* 0.95, CH_2Cl_2) for **1** of >98% ee}, identical in all respects to that previously described.[12,14]



In summary, the chiral base-mediated rearrangement of an epoxide (*trans*-**6** → **8**) is the key step in a new route to amino alcohol **1**, an important intermediate in the synthesis of the cyclopentene fragment of nucleoside Q, carbocyclic nucleoside analogues and neoplanacin A. A range of other stereodefined, functionalised cyclopentenyl amine building blocks have also been prepared.

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