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2-Azabicyclo[2.2.1]hept-5-en-3-one Epoxide: A Versatile Intermediate for the Synthesis of Cyclopentyl Carbocyclic 2-Deoxy-, 3-Deoxy- & *Ara*- Ribonucleoside Analogues.

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Abstract: 5,6-Epoxy-*exo*-2-azabicyclo[2.2.1]heptan-3-one has been used as a versatile intermediate in the synthesis of 2-deoxy-, 3-deoxy- and *ara*- cyclopentyl carbocyclic nucleosides. An efficient, short synthesis of the (+) carbocyclic thymidine **13** is reported.

The potent antiviral and antitumour properties shown by carbocyclic nucleosides[1-3] has stimulated considerable interest in efficient homochiral synthetic routes.[4] Several groups have reported the use of 2-azabicyclo[2.2.1]hept-5-en-3-one **1** as a key starting point for the synthesis of carbocyclic sugars and nucleosides.[4-7] The commercial availability of both pure enantiomers of this bicyclic lactam provides direct entry into homochiral intermediates and products. We report here careful investigations of the epoxidation of 2-azabicyclo[2.2.1]hept-5-en-3-one **1** and the elaboration of this epoxide into intermediates suitable for the synthesis of 2-deoxy-, 3-deoxy- and *ara*- cyclopentyl carbocyclic nucleosides.

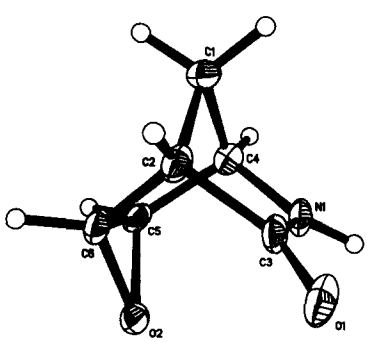

Figure 1: *Endo* epoxide **3**

Legraverend *et al.* described the epoxidation of **1** using oxone (potassium peroxymonosulfate) in aqueous methanol under carefully controlled pH conditions, giving exclusively the *exo* epoxide **2** in good yield.[8] Furthermore, they claim the epoxidation of **1** with *meta*-chloroperbenzoic acid (MCPBA) gives very poor yields of the epoxide **2**. In our hands the epoxidation of **1** with oxone leads to a mixture of the *exo* and *endo* epoxides **2** and **3** in a 3:1 ratio and in rather modest yield (Scheme 1). Definitive proof that the *endo* epoxide **3** is indeed produced was obtained by X-ray crystallography of the crystalline material[9] isolated by column chromatography (Figure 1). It is possible that the differences in yield are a reflection of variations in the pH during the reaction. Certainly any adventitious ring-opening of the epoxide would lead to a polar product which

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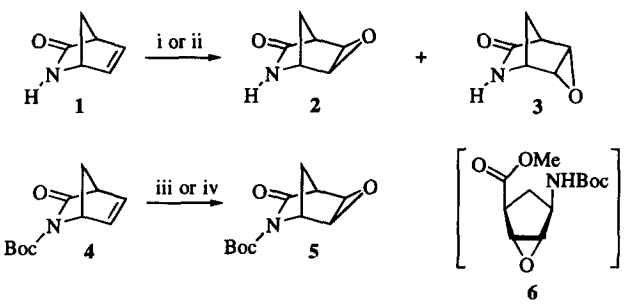
would not extract into dichloromethane. It is less easy to understand how the facial selectivity would be influenced by pH. The *endo* epoxide **3** is readily removed by crystallisation and this might explain why it has not been reported previously. MCPBA epoxidation of **1** in our hands gives a good yield (85%) of the epoxides **2** [(±) **2** m.p. (CH_2Cl_2) 120-121 °C, lit.[8] 120 °C] and **3** [(±) **3** m.p. (Et_2O:EtOAc) 144-145 °C], in a ratio of 7:1 from which the pure *exo* epoxide **2** can be readily obtained by recrystallisation. In contrast to previous reports, MCPBA epoxidation appears to be the preferred method for preparing the epoxide of the bicyclic lactam **1**.

Scheme 1



1 **2** **3** **4** **5** **6**

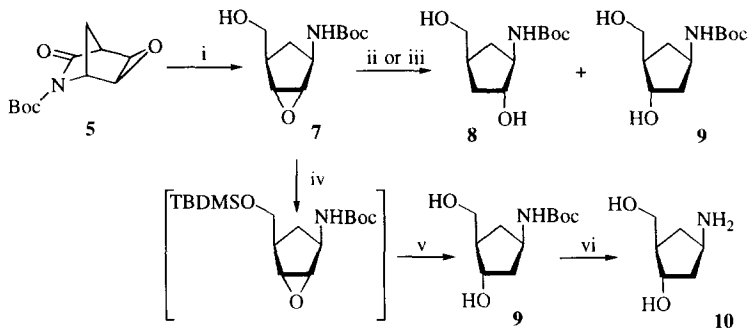
Reagents and conditions: (i) Oxone, MeOH, KOH (1M), **2&3** 3:1 45 %; (ii) MCPBA, CH_2Cl_2, **2&3** 7:1 85 %; (iii) Oxone, MeOH, KOH (1M), **5&6** 86 %&13 %; (iv): MCPBA, CH_2Cl_2, **5** 71 %.

In view of the lack of complete facial selectivity observed in the epoxidation of **1**, the corresponding epoxidation of the N-Boc derivative **4** was investigated. The N-Boc bicyclic lactam **4** has been previously reported[10,11] and was prepared by treatment of **1** with Boc anhydride. Epoxidation of **4** with MCPBA gave exclusively the *exo* epoxide **5** in excellent yield, in agreement with Katagiri *et al.* (Scheme 1).[7] Attempted epoxidation of **4** with oxone under the conditions described by Legraverend *et al.*[8] for **1** gave rise to a mixture containing the bicyclic lactam **5** [(±) **5**: m.p.(hexane:Et_2O) 115-116 °C, lit.[7] 123-125 °C; (-) **5**: $[\alpha_D]^{24}$ -94.58 (c 0.7, CH_2Cl_2), m.p. (hexane:Et_2O) 122-123 °C] and the ring-opened cyclopentane derivative **6**, due to the competing methanolysis of the lactam functionality.

Despite the ready availability of epoxides **2** and **5** it is surprising that there appear to be no reports of attempts to access cyclopentyl 2' and 3'-deoxyribose analogues by reductive ring-opening of either of these epoxides. Katagiri *et al.* had previously reported the facile reductive ring-opening of the N-acyl derivatives of the bicyclic lactam **1**.[6] Using a wide range of reducing agents we have observed that the lactam is considerably more susceptible to reduction than the epoxide, confirming the observations of Katagiri *et al.*.[7] Thus, reduction of the bicyclic lactam **5** to the corresponding cyclopentyl epoxide **7** was readily achieved with sodium borohydride at 0 °C. The availability of **7** [(±) **7**: m.p.(CH_2Cl_2:light petroleum ether) 116-117 °C, lit.[7] 118-119 °C; (+) **7**: $[\alpha_D]^{24}$ +23.13 (c 0.6, CH_2Cl_2), m.p. (CH_2Cl_2:light petroleum ether) 126-127 °C] allowed us to explore regiocontrol of the reductive cleavage of the epoxide functionality. Treatment of **7** with Dibal-H in THF gave a mixture of the two regioisomers **8** [(±) **8** m.p. (Et_2O:light petroleum ether) 80-81 °C] and **9** [(±) **9**: m.p.(EtOAc:light petroleum ether) 104-105 °C; (+) **9**: $[\alpha_D]^{24}$ +4.27 (c 0.4, $CHCl_3$), m.p. (EtOAc:light petroleum ether) 129-130 °C] in a ratio of 1:1 in relatively low yield. The use of Red-Al in toluene gave **8** and **9** in a ratio

of 3:1 in 71% yield, which represents a convenient route to carbocyclic 3'-deoxyribose analogues (Scheme 2). In view of the fact that the regioselectivity of the ring-opening of epoxide **7** appeared to respond to steric effects of the reducing agent, we reasoned that attack of the reducing agent at the 3'-carbon would be favoured if a bulky protecting group was introduced at the 5'-hydroxyl group. Reaction of **7** with *t*-butyldimethylsilyl triflate followed by reduction with Red-Al in toluene gave **9** as the sole product (85 % yield). Although the silyl protecting group is removed during the reduction reaction, it clearly is in place at the stage of the hydride delivery since total control of the regiochemistry is observed. Hydrolysis of **9** by heating in water afforded the carbocyclic 2'-deoxyribose analogue **10** ((+)-(1*R*,2*S*,4*R*)-4-amino-2-hydroxy-1-hydroxymethyl cyclopentane) [(+) **10:** $[\alpha_D]^{17}$ +20.68 (c 1.0, DMF), lit.[12] $[\alpha_D]^{25}$ +33 (c 1.0, DMF)] by a route that is convenient alternative to that reported by Bray *et al.* (Scheme 2).[5]

Scheme 2

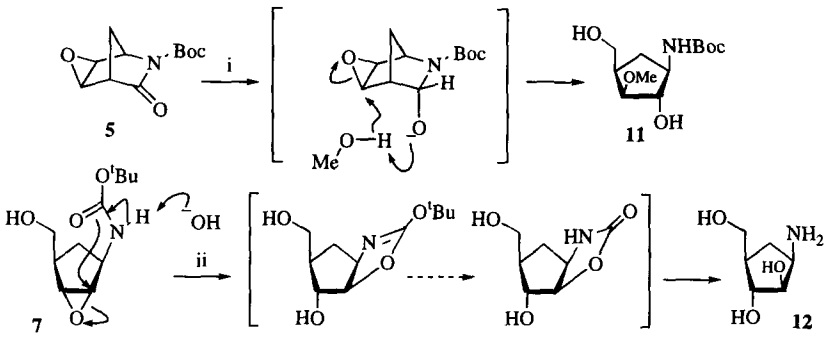


Reagents and conditions: (i) $NaBH_4$, MeOH, **7** 89 %; (ii) Dibal-H,THF, 1:1 **8&9** < 25 %; (iii) Red-Al, toluene, **8&9** 3:1 71 %; (iv) TfOTBDMS, 2,6-lutidine, CH_2Cl_2 97 %; (v) Red-Al, toluene, **9** 85 %; (vi) H_2O, reflux, **10** quant. %.

We have undertaken a limited investigation of ring-opening of some of the epoxides with different nucleophiles. The bicyclic lactam epoxide **5** when treated with $NaBH_4$ in methanol at 50 °C, led not only to reductive cleavage of the lactam but also to the regioselective methanolysis of the epoxide by attack at the 3'-position to give **11** (Scheme 3). A stereocomplementary ring-opening of the epoxide ring of **7** with an oxygen nucleophile was achieved by treatment with aqueous sodium hydroxide (1M) at 75 °C which afforded the carbocyclic *ara*-ribose analogue **12** as the sole product (62% yield) (Scheme 3). This complementary regioselectivity is intriguing. The base hydrolysis of **7** to give **12** almost certainly proceeds *via* participation of the N-Boc functionality as shown in Scheme 3. A similar participation has been reported by Katagiri *et al.* in the BF_3-catalysed ring opening of epoxide **7**.[7] The mechanistic explanation for the opposite regioselectivity of the methanolysis of the epoxide during the reduction of **5** is less clear although it may involve one of the intermediates in the reductive cleavage of the lactam serving as a general base to promote methoxide attack at the 3'-position (Scheme 3).

We are interested in the biological properties of hybrid oligonucleotides containing carbocyclic nucleoside residues at defined positions. The aminodiol **10** was converted into the corresponding (+)carbo-

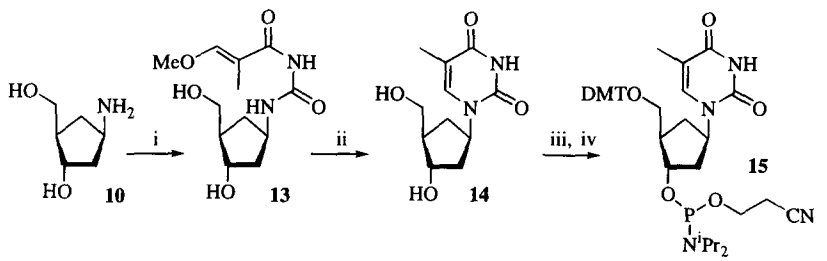
Scheme 3



Reagents and conditions: (i) $NaBH_4$, MeOH 50 °C, **11** 85 %; (ii) NaOH (1 M), HCl (1 M) **12** 62 %.

cyclic thymidine derivative **14** [(±) **14**: m.p.(MeOH) 219-220 °C, lit.[13] 219-221.5 °C; (+) **14**: $[\alpha_D]^{21}$ +2.14 (c 1.0, MeOH), m.p. (MeOH) 167-168 °C, lit.[12] 168-169 °C] by standard literature methods.[14] The preparation of the corresponding phosphoramidite **15**, suitable for automated oligonucleotide synthesis, was also achieved in good yield in two further steps from **14** (Scheme 4). The corresponding 3'-deoxy and *ara*-nucleosides are available from similar conversion of intermediates **8** and **12**.

Scheme 4



Reagents and conditions: (i) CH(OMe)C(Me)CONCO, DMF:Et_2O 3:1, **13** 75 %; (ii) NH_3, reflux, **14** 83 %; (iii) DMTrCl, pyridine, 65 %; (iv) Cl-P(OCH_2CH_2CN)N(iPr)$_2$, EtN(*i*Pr)$_2$, CH_2Cl_2, **15** 67 %.

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9. (±) **3**: m.p. (from Et_2O:EtOAc) 144-145 °C. Found: C, 57.3; H, 5.1; N, 11.0. $C_6H_7O_2N$ requires C, 57.5; H, 5.6; N, 11.2. δ_H(400 MHz; $CDCl_3$) 6.03 (1H, br s, NH), 3.93 (1 H, br t, $J_{1,6}$ 3.7, H-1), 3.87-3.85 (2 H, m, H-6, 5), 2.79 (1 H, d, $J_{4,7}$ 1.8, H-4), 2.34 (1 H, d, $J_{7s,a}$ 9.2, H-7s), 2.22 (1 H, ddd, $J_{7a,s}$ 9.2, $J_{7a,4}$ 1.8, $J_{7a,1}$ 1.6, H-7a); δ_C(100.6 MHz; $CDCl_3$) 177.06 (C=O), 58.02(C-6), 54.02 (C-1), 53.57 (C-5), 52.01 (C-7), 46.00 (C-4). m/z (EI) 125.04769 (M^+), requires 125.04768. ν_{max}(sol.)/cm^{-1} 3420*m* (N-H), 3020-2990*w* (C-H), 1730*s* (C=O), 1030*s* (C-O). Full details of the X-ray structure will be published in the full paper.
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