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An Application of Quinic Acid to the Synthesis of Cyclic Homochiral Molecules: A Common Route to Some Interesting Carbocyclic Nucleoside Precursors.

Christopher D. Maycock*
Centro de Espectrometria de Massa, Complexo I,
Avenida Rovisco Pais, 1096 Lisboa and Faculdade de Ciências da Universidade de Lisboa, Departamento de Química
Rua Ernesto de Vasconcelos, 1700 Lisboa, PORTUGAL.

M. Teresa Barros
António G. Santos
Faculdade de Ciências e Tecnologia da Universidade Nova de Lisboa, Departamento de Química
2825 Monte da Caparica and Centro de Tecnologia Química e Biológica, Rua de Quinta Grande 6, Apartado 127, 2780 Oeiras,.

Lício S. Godinho
Faculdade de Ciências e Tecnologia da Universidade Nova de Lisboa, Departamento de Química
2825 Monte da Caparica.

Abstract: A cyclopentane derivative elaborated from (-)-quinic acid has been converted efficiently and stereoselectively into several cyclopentylamines, precursors to carbocyclic nucleosides which have previously been shown to be biologically interesting

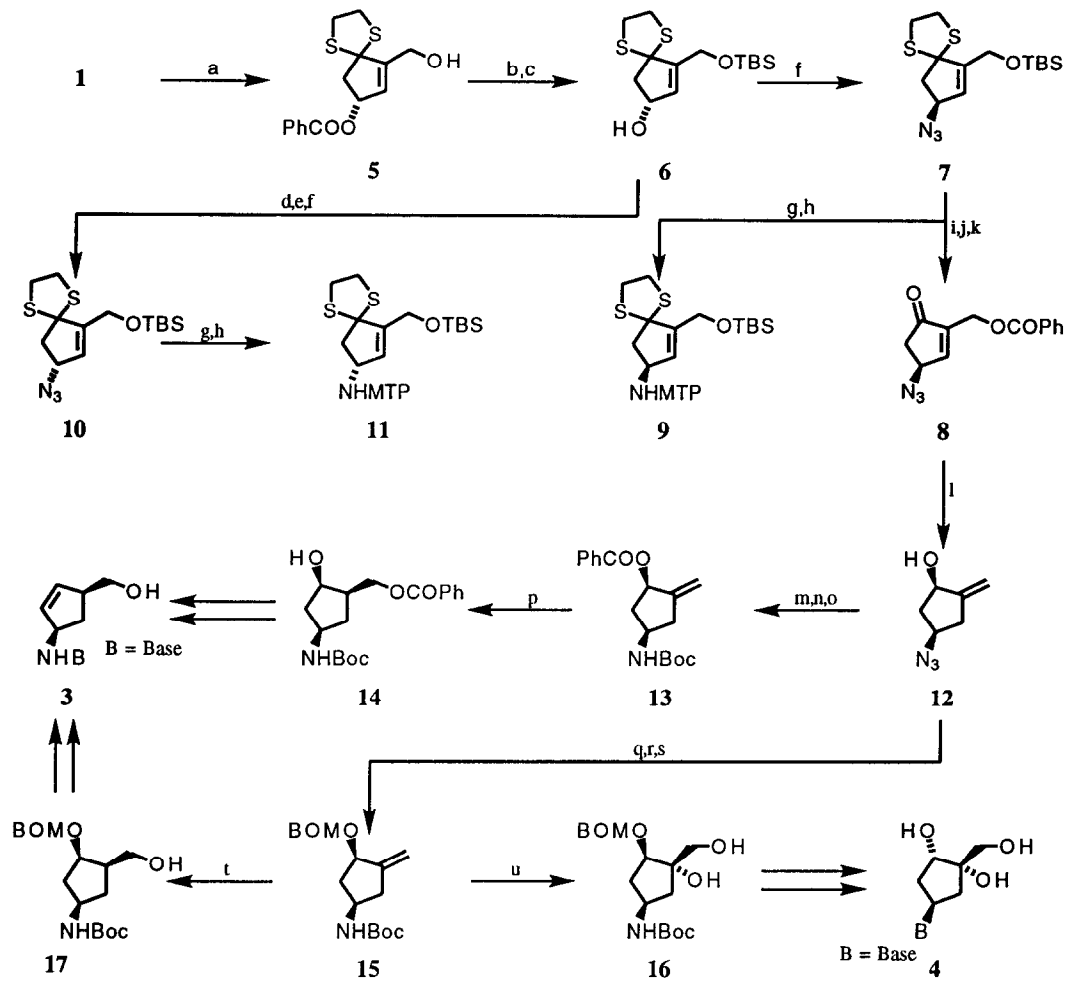
Recent reviews[1] on the subject of nucleoside synthesis and their activity as agents in the fight against the HIV and other viruses have highlighted the importance of their carbocyclic analogues as possible treatments for AIDS. Carbovir **3** (B=guanine)[1,2] has been the target of several research groups because of its high antiviral activity. Other polysubstituted cyclopentane derivatives, such as **4** (B=guanine), also show promise against herpes[1,3].

1 **2** R = PhCO or BOM **3** B = Base **4**

Scheme 1.

Many of the syntheses of these compounds have been carried out by the chemical manipulation of other nucleosides themselves often not readily available. The two approaches to the total synthesis of such compounds, linear and convergent approaches, often involve very different strategies. We report here our approach (scheme 1) which relies upon the availability of the key intermediates **2**.

As part of our studies related to the utility of quinic acid **1** in synthesis[4] we have applied a successful strategy for the synthesis of precursors to carbocyclic nucleosides using essentially the linear approach. The strategy can however be applied to convergent syntheses since the base could be incorporated using similar technologies to those applied here Compound **5** $[\alpha]_D^{20}$= +166.6, (c=4.55, CH_2Cl_2), was prepared by a



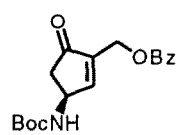
Scheme 2. (a) See references 4-14. (b) TBDMSCl, Et_3N, DMAP, 3h, 25°C, 98% (c) KOH, Methanol, 1h, 25°C, 95%. (d) Ph_3P, DEAD, $PhCO_2H$, THF, 1h, 25°C, 94% (e) KOH, Methanol, 1h, 25°C, 94%. (f) Ph_3P, DEAD, HN_3, THF, 30mın, 25°C, 88%. (g) 1,3-Propanedithiol, Et_3N, 18h, 25°C, 87% (h) MTPCl, Pyridine/CCl_4, DMAP, 0°C, 1h, 75% (i) Bu_4NF, THF, 20min, 25°C, 98%. (j) PhCOCl, Pyridine, DMAP, 1 5h, 25°C, 95% (k) $(PhSeO)_2O$, Propylene oxide, THF, 18h, 25°C, 76%. (l) $NaBH_4$, Ethanol, 1h, 0°C, 95%. (m) PhCOCl, Pyridine, DMAP, 1h, 25°C, 97% (n) 1,3-Propanedithiol, Et_3N, 18h, 25°C, 92%. (o) Boc_2O, $(i\text{-}Pr)_2NEt$, $CHCl_3$, 2h, reflux, 91% (p) ı) 9-BBN, THF, 2h, 25°C, ıı) Ethanol, NaOH, H_2O_2, 1h, 50°C, 81%. (q) $PhCH_2OCH_2Cl$, $(i\text{-}Pr)_2NEt$, 8h, 25°C, 95%. (r) 1,3-Propanedithiol, Et_3N, 18h, 25°C, 94% (s) Boc_2O, $(ı\text{-}Pr)_2NEt$, $CHCl_3$, 2h, refluxo 90% (t) i) 9-BBN, THF, 2h, 25°C, ıı) NaOH, H_2O_2, 1h, 50°C, 82% (u) OsO_4, NMO, 4h, 25°C, 92%.

combination of methods available in the literature[5-14]. The primary hydroxyl group was protected as its TBDMS ether and the benzoate ester cleanly hydrolysed to afford the alcohol **6** $[\alpha]_D^{20}$= +33.0, (c=3.75, CH_2Cl_2).

Contrary to that reported in the literature[15], a Mitsunobu azide modification on compound **6** proceeded very rapidly (the reaction was complete in about 10min.) and cleanly at the allylic alcohol producing the azide **7** $[\alpha]_D^{20}$= -147.1±0.1, (c=5.16, CH_2Cl_2). By double inversion using the very efficient Mitsunobu technology we produced compound **10** $[\alpha]_D^{20}$= +146.8±0.1, (c=3.11, CH_2Cl_2) the enantiomer of **7.** Both compounds **7** and **10** were reduced to the corresponding amines using 1,3-propanedithiol[16] and converted to their Mosher amides **9** and **11.** Analysis of the NMR spectra of the separate and mixed diastereoisomers indicated that the products were >99% optically pure. Thus both enantiomeric series were available.

Silyl ether **7** was efficiently converted to the benzoate **8** $[\alpha]_D^{20}$= -99.1±0.1, (c=2.63, CH_2Cl_2) using TBAF[17] followed by benzoylation and removal of the dithioacetal with phenylseleninic anhydride[18]. Other common reagents were unable to effect the latter transformation. Compound **8** contains almost all of the structural features necessary for the elaboration of members of the Neplanocin family of compounds. We did not study this possibility as we were more interested in saturated carbocycles which could serve as precursors for a wide range of derivatives. Reduction with borohydride at 0°C produced only alcohol **12** $[\alpha]_D^{20}$= -70.5±0.1, (c=2.05, CH_2Cl_2) in high yield. Amide **13** $[\alpha]_D^{20}$= -17.2, (c=1.05, CH_2Cl_2) was prepared from **12** in three steps. The reduction of the azide was effected using propanedithiol/TEA a cleaner reducing agent than the Staudinger, phosphinimine, method. Hydroboration of **13** with 9-BBN[19] followed by oxidation resulted in a totally regio- and stereoselective formation of benzoate **14** $[\alpha]_D^{20}$= -27.2±0.1, (c=0.53, CH_2Cl_2) in which the benzoyl group had migrated to the primary alcohol under the reaction conditions. It is interesting that this ester was not hydrolysed under the oxidation conditions. Careful control of the amount of hydroxide used is essential and the use of an excess leads to the formation of the corresponding diol. We have noted that the reaction mixture is rapidly neutralised by the formation of borate salts.

Alternatively the benzyloxymethyl ether of alcohol **12** could be prepared and converted to the amide **15** $[\alpha]_D^{20}$= -14.6±0.1, (c=6.48, CH_2Cl_2). This compound could be converted with total stereochemical control to the primary alcohol **17** $[\alpha]_D^{20}$= -62.9±0 1, (c=1.13, CH_2Cl_2) using hydroboration/oxidation. In this way we could predetermine which hydroxyl group would remain protected for further reactions. Dihydroxylation using catalytic osmium tetroxide with NMO as reoxidant[20] afforded exclusively the diol **16** $[\alpha]_D^{20}$= -44.7, (c=6.97, CH_2Cl_2). Using methods already published[1] it should be possible to convert compounds **14** or **17** to carbovir **3** and compound **16** to the herpes active triol **4**



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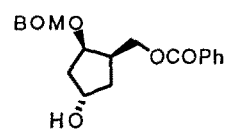

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In this paper we demonstrate the use of quinic acid for the synthesis of aminocyclopentane derivatives useful for the synthesis of carbocyclic nucleosides such as carbovir **3** and anti herpes agent **4.** We predict that the use of a convergent strategy, direct substitution of the hydroxyl group of **5** by a suitable base, would be a more efficient way of synthesising these molecules. In preliminary studies we have noted that the reduction of **18** with borohydride does not proceed with the same stereochemical control observed for the azide **8.** Thus it may not be possible to achieve high selectivities for similar reactions with analogues of compound **8.** We have studied this very important reduction-elimination reaction with other cyclopentenone substrates and our results will be published shortly. An alternative, convergent route, would involve the substitution of the hydroxyl group of **19,** a compound readily available from quinic acid[21], by a suitably nucleophilic base.

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