Diastereoselective Synthesis of a Precursor of Homocarbocyclic Nucleosides

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A convenient diastereoselective synthesis of an immediate precursor for a rapid access to a variety of homo-carbocyclic nucleosides, is described. The synthetic scheme involves a high yielding new type of Pd(0) catalyzed cyclization of a suitable hydrazine derivative together with a stereospecific OsO_4 triggered dihydroxylation step.

Introduction

During the past few years the carbocyclic analogues of nucleosides have received much attention since a great number of compounds in this series exhibit remarkable antitumor and antiviral activities.[1] Moreover, it has been established that a few closely related molecules manifest a promising anti-parasitic activity.[2] It is also of interest to note that, for therapeutical uses, these compounds are endowed with a greater metabolic stability, compared to normal nucleosides, which is a potential advantage. In particular, they can avoid the degradation pathway mediated by phosphorylases which cleave the glycosidic bond of nucleosides.[3] One should also mention the new applications which are emerging for carbocyclic nucleosides in the field of therapeutical oligonucleotides.[4]

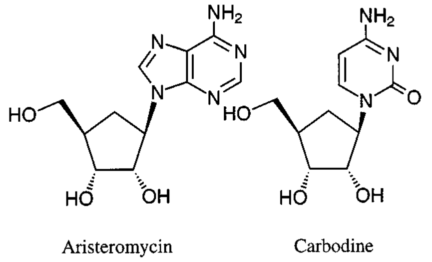
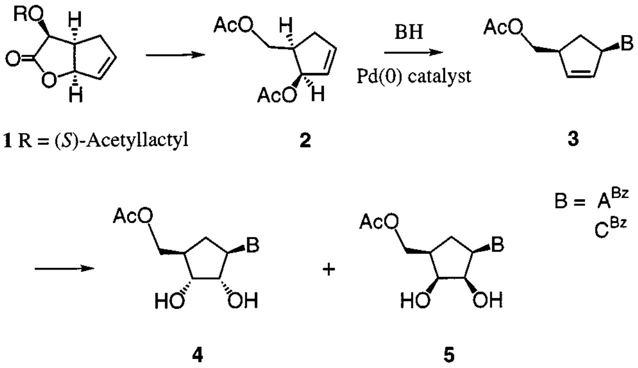


Figure 1

From the chemistry viewpoint a great number of methodologies, which can be classified into two categories, have been designed to obtain these nucleoside analogues in high yields. In one case the heterocyclic base is introduced directly onto the carbocyclic moiety. On the other hand, more general but less convergent approaches involve the initial synthesis of a functionalized cyclopentylamine which is then further modified to construct the heterocyclic part.[1]



Scheme 1

Recently, we have developed a convergent route to aristeromycin and carbodine[5] (Figure 1) which is outlined in Scheme 1. This method makes use of the optically active lactone **1** which can be prepared in significant amounts and easily transformed into the diacetate **2** in a few simple steps.[6][7] Unfortunately, this synthetic scheme suffers a limitation since the dihydroxylation reaction carried out with **3** as the substrate led to a mixture of the α- and β-diols, **4** and **5**, respectively. Despite many efforts, we were unable to find satisfactory conditions which would enhance the stereoselectivity of the reaction to favour the ribose configuration. It occurred to us that a solution to this problem would be to dihydroxylate either a bicyclic system, or to develop a substrate showing high facial stereoselectivity.[8] Finally, we designed the route shown in Scheme 2 which, starting from **6**,[1] led stereospecifically to the cyclopentyl derivative **12** which can be considered as an immediate precursor of homocarbocyclic nucleosides.[9]

Results and Discussion

The synthesis of the target compound **12** was carried out in nine steps starting from acetate **6**.[7] Thus, acetylation of the crude product resulting from the treatment of acetate **6** with hydrazine hydrate gave the tetraacetate **7** in high yield. We were pleased to find that, in the presence of Pd(0) cata-

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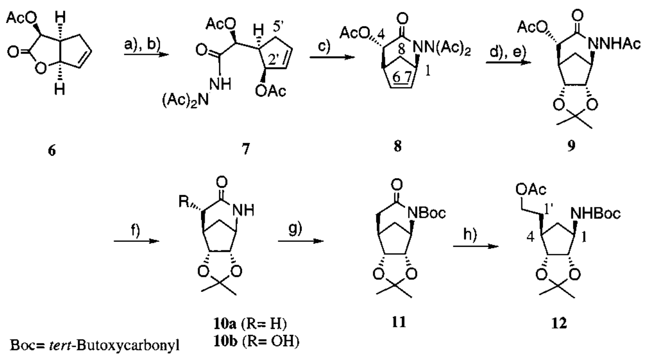

Scheme 2. a) NH_2NH_2,H_2O, ethanol, 80° C, 4 h; b) Ac_2O, pyridine, room temp., 2 h; c) $Pd(PPh_3)_4$, THF, room temp., 24 h; d) Trimethylamine *N*-oxide, cat. OsO_4, acetone, room temp., 3 h; e) Acetone, dimethoxypropane, CSA, room temp., overnight; f) Li/NH_3, THF, 1 h; g) Boc_2O, DMAP, MeCN, room temp., 24 h; h) $NaBH_4$, H_2O/MeOH, room temp., overnight then Ac_2O, pyridine, room temp., 2 h

lyst, this compound was cyclized very efficiently at room temperature to yield the cyclic derivative **8**. To the best of our knowledge this reaction is unprecedented since we are not aware of any example of such a reaction involving a hydrazine derivative. Interestingly, all attempts to observe the same type of cyclization using the corresponding benzylamide failed whatever the reaction conditions.[10] In any case, compound **8** was an ideal substrate to perform an osmium-tetroxide-mediated stereospecific dihydroxylation reaction. Indeed, using standard conditions a single diol was obtained which was subsequently protected with an isopropylidene group to give the mono-acetyl derivative **9** in 65% combined yield for the two steps. At this stage we were faced with the problem of the reductive cleavage of both the N−N bond together with the elimination of the acetoxy group. This crucial step was accomplished by means of a Li/NH_3 reduction reaction[11] to give amides **10a** and **10b** both in a moderate 45% yield. Treatment of amide **10a** with Boc_2O gave the expected fully protected derivative **11** which readily underwent a $NaBH_4$/LiCl triggered reduction to form an alcohol intermediate which was subsequently acetylated to give **12** in excellent overall yield.

In summary, we have described a convenient diastereoselective method for the preparation of an aminocyclopentyl derivative which might be useful for providing a rapid access to a variety of homocarbocyclic nucleosides analogues. Indeed, the presence of an amino function (which can be easily chemoselectively deprotected) in this intermediate should serve to further elaborate various modified heterocyclic bases which, hopefully, might confer to these molecules an interesting level of biological activity as currently observed in this series

Experimental Section

General: Solvents were dried by standard methods. − All reagents were of commercial quality (Acros, Aldrich or Lancaster) and were used without further purification. − Melting points were taken using a Reichert apparatus and are uncorrected. − Microanalyses were performed by the "Service de Microanalyses de l'ICSN-CNRS". − ^1H and ^{13}C NMR: Bruker AC200, AC250 and AM300 instruments. Chemical shifts are δ values downfield from internal TMS (^1H, ^{13}H). − Mass spectrometry: AEI MS50 (EI); AEI MS9 (CI). − Flash chromatography: 32−63 mm silica-gel (SDS). − Thin layer chromatography: Silica gel 60 F_{254} coated sheets (SDS).

***N,N*-Diacetyl[*cis*-2-acetoxy-2-(2′-acetoxycyclopent-3′-enyl)]acetic Acid Hydrazide (7):** Hydrazine hydrate (1.2 mL, 23 mmol) was added to a solution of 4-*endo*-acetoxy-2-oxabicyclo(3.3.0)oct-7-en-3-one (**6**) (3.72 g, 21 mmol) in ethanol (25 mL). The mixture was stirred at 80 °C for 4 h. The solvent was then removed in vacuo, the residue redissolved in pyridine (15 mL) and acetic anhydride (15 mL) added. After stirring for 2 h the reaction mixture was concentrated in vacuo and the residue purified by silica gel column chromatography (ethyl acetate/heptane, 50:50) to give compound **7** (4.95 g, 70%). m.p. 93−97 °C (ethyl acetate/heptane). − ^1H NMR ($CDCl_3$, 250 MHz): δ = 8.22 (s, 1 H, NH), 6.18 (m, 1 H, H-4′), 5.9 (m, 1 H, H-3′), 5.76 (m, 1 H, H-2′), 5.31 (d, *J* = 11.2 Hz, 1 H, H-2), 2.91 (m, 1 H, H-1′), 2.47 (m, 2 H, H-5′), 2.39 [s, 6 H, $N(Ac)_2$], 2.14 (s, 3 H, Ac), 1.97 (s, 3 H, Ac). − ^{13}C NMR ($CDCl_3$, 62 MHz): δ = 171.2, 170.8, 170.3, 169.4, 138.0, 129.1, 77.3, 71.9, 41.8, 33.2, 24.9, 21.0, 20.6. − CI-MS (NH_3) *m*/*z*: 358 [$(M + H)^+ + NH_3$]. − $C_{15}H_{20}N_2O_7 \cdot 0.25H_2O$ (244.74): calcd. C 52.38, H 5.99, N 8.12; found C 52.29, H 5.81, N 8.31.

4-*exo*-Acetoxy-2-diacetylamino-2-azabicyclo[3.2.1]oct-6-en-3-one (8): To a solution of **7** (1.39 g, 4.08 mmol) in THF (20 mL) under an argon atmosphere, was added $Pd(PPh_3)_4$ (231 mg, 0.2 mmol). The reaction mixture was stirred at room temp. during 24 h. The solvent was removed in vacuo and the residue purified over a silica gel column (ethyl acetate/heptane, 35:65) to give compound **8** (1.05 g, 92%). m.p. 86−88°C (ethyl acetate/heptane). − ^1H NMR ($CDCl_3$, 250 MHz): δ = 6.22 (m, 1 H, H-6), 5.83 (m, 1 H, H-7), 5.60 (d, *J* = 9.3 Hz, 1 H, H-4), 4.64 (m, 1 H, H-1), 3.48 (m, 1 H, H-5), 2.52 (s, 3 H, Ac), 2.49 (m, 2 H, H-8), 2.19 (s, 6 H, $N(Ac)_2$). − ^{13}C NMR ($CDCl_3$, 62 MHz): δ = 172.8, 170.0, 169.0, 139.5, 127.0, 69.6, 65.6, 38.5, 31.8, 26.2, 23.5, 20.6. − EI-MS *m*/*z*: $[M]^+$ 280. − $C_{13}H_{16}N_2O_5$ (280.28): calcd. C 55.72, H 5.76, N 10.00; found C 55.82, H 5.83, N 9.91.

4-*exo*-Acetoxy-2-acetylamino-6,7-*exo*-isopropylidenedioxy-2-azabicyclo[3.2.1]octan-3-one (9): To a solution of **8** (3.67 g, 3.09 mmol) in acetone (5 mL) was added *N*-trimethylamine oxide (2.19 g, 19.74 mmol) in 5 mL water. To the cooled solution (−78 °C) was added a chip of OsO_4 and the mixture was stirred at room temp. for 3 h. The solution was filtered over Celite which was then carefully washed with a solution of CH_2Cl_2/methanol (9:1). Then the combined filtrates were evaporated and the residue placed on the top of a silica gel column. Elution with a mixture of CH_2Cl_2/methanol (92:8) gave a diol (2.88 g, 81%) as a foam. This compound was dissolved in acetone (20 mL) containing dimethoxypropane (2 mL) and camphor sulfonic acid (350 mg, 1.5 mmol) and the solution was stirred overnight at room temp. Then the solvent was removed in vacuo and the residue was purified by silica gel column chromatography (CH_2Cl_2/methanol, 97:3) to give compound **9** (2.65 g, 65%, for the 2 steps) as a white foam. − ^1H NMR ($CDCl_3$, 250 MHz): δ = 8.48 (s, 1 H, NH), 5.55 (d, *J* = 7.67 Hz, 1 H, H-4), 4.76 (m, 1 H, H-1), 4.54 (d, *J* = 5.2 Hz, 1 H, H-7), 4.00 (d, *J* = 5.8 Hz, 1 H, H-6), 3.47 (m, 1 H, H-5), 2.15 (s, 3 H, Ac), 2.07 (s, 3 H, Ac), 1.97 (m, 2 H, H-8), 1.42 (s, 3 H, Me), 1.29 (s, 3 H, Me). − ^{13}C NMR ($CDCl_3$, 62 MHz): δ = 170.2, 169.4, 110.7, 81.8, 81.3, 70.4, 68.1, 39.1, 31.8, 26.6, 24.3, 20.9, 20.7. − EI-MS: *m*/*z*: 312 $[M]^+$. − $C_{14}H_{20}N_2O_6 \cdot 0.5H_2O$ (321.33): calcd. C 52.36, H 6.59, N 8.72; found C 52.71, H 6.55, N 8.55.

6,7-*exo*-Isopropylidenedioxy-2-azabicyclo[3.2.1]octan-3-one (10): To liquid ammonia (5 mL) containing pieces of Li (≈50 mg) was added compound **9** (1.24 g, 3.97 mmol) in THF (5 mL). After stirring for 1 h, the ammonia was evaporated and NH_4Cl (1.70 g, 32 mmol) in water (3 mL) was added to the solution. The resulting mixture was diluted with water and the aqueous phase extrated with ethyl acetate (3 × 50 mL). The combined organic phase was dried and evaporated in vacuo to give a residue which was purified by silica gel column chromatography using a gradient of methanol in CH_2Cl_2 (1 to 5%) to give compound **10a** as white crystals (352 mg, 45%). m.p. 138−141 °C (methanol/CH_2Cl_2, 1:9) and **10b** (380 mg, 45%) as a foam.

10a: ^1H NMR ($CDCl_3$, 200 MHz): δ = 6.50 (s, 1 H, NH), 4.74 (t, 1 H, H-1), 4.44 (d, 1 H, *J* = 5.2 Hz H-7), 3.92 (d, 1 H, *J* = 6.3 Hz, H-6), 3.10 (m, 1 H, H-5), 2.54 (dd, 1 H, *J* = 7.7 Hz and *J* = 17.0 Hz, H-4), 2.30 (dd, 1H *J* = 7.5 Hz and 14.5 Hz, H-8), 2.10 (d, 1 H, *J* = 17.0 Hz, H-4′), 1.67 (m, 1 H, H-8′), 1.44 (s, 3 H, Me), 1.29 (s, 3 H, Me). − ^{13}C NMR ($CDCl_3$, 62 MHz): δ = 177.7, 110.5, 84.7, 81.9, 66.1, 37.8, 37.1, 36.6, 26.7, 24.3. − CI-MS (*i*BuH): *m*/*z*: 198 [(M + H)$^+$]. − $C_{10}H_{15}NO_3$·O.5 H_2O (206.25): calcd. C 58.24, H 7.81, N 6.79; found C 58.29, H 7.31, N 6.78.

10b: ^1H NMR ($CDCl_3$, 200 MHz): δ = 6.26 (s, 1 H, NH), 4.76 (t, 1 H, *J* = 4.6 Hz, H-1), 4.43 (m, 2 H, H-4, H-7), 3.82 (d, 1 H, *J* = 5.8 Hz, H-6), 3.34 (m, 1 H, H-5), 2.26−1.80 (m, 2 H, 2 × H-8), 1.45 (s, 3 H, Me), 1.29 (s, 3 H, Me). − ^{13}C NMR ($CDCl_3$, 62 MHz): δ = 178.1, 111.2, 85.8, 82.8, 72.0, 62.6, 44.1, 32.0, 26.8, 24.4. − CI-MS (*i*BuH): *m*/*z*: 214 [(M + H)$^+$]. − $C_{10}H_{15}NO_4$·0.25 H_2O (217.74): calcd. C 55.16, H 7.17, N 6.46; found C 55.09, H 6.77, N 6.69.

***N*-2-*tert*-Butoxycarbonyl-6,7-*exo*-isopropylidenedioxy-2-azabicyclo-[3.2.1]octan-3-one (11):** To a solution of **10a** (173 mg, 0.88 mmol) in acetonitrile (10 mL) was added Boc_2O (212 mg, 0.97 mmol) and 4-dimethylaminopyridine (DMAP) (11 mg, 0.09 mmol). The mixture was stirred at room temp. for 24 h. The solvent was removed in vacuo and the residue was purified by silica gel colunm chromatography (ethyl acetate/heptane, 25:75) to give the desired compound **11** (208 mg, 80%) as a white solid. m.p. 115−119° C (ethyl acetate/heptane). − ^1H NMR ($CDCl_3$, 250 MHz): δ = 4.67 (m, 1 H, H-1), 4.59 (d, *J* = 5.2 Hz, 1 H, H-7), 4.20 (d, *J* = 7.2 Hz, 1 H, H-6), 2.98 (m, 1 H, H-5), 2.69 (m, 1 H, H-4), 2.32 (m, 2 H, H-8, H-4′), 1.61 (m, 1 H, H-8′), 1.56 (s, 9 H, Boc), 1.46 (s, 3 H, Me), 1.31 (s, 3 H, Me). − ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 173.2, 150.0, 110.4, 85.4, 83.2, 80.6, 69.6, 37.5, 37.1, 31.7, 27.8, 26.6, 24.3. − IE-MS: *m*/*z*: (M) 297. − $C_{15}H_{23}NO_5$ (297.36): calcd. C 60.59, H 7.80, N 4.71; found C 60.52, H 7.72, N 4.61.

4-Acetoxyethyl-1-*N*-*tert*-butyloxycarbonylamino-2,3-isopropylidenedioxycyclopentane (12): To a solution of **11** (454 mg, 1.53 mmol) in a mixture of water (2 mL) and methanol (3 mL) cooled to 0°C was added $NaBH_4$ (61 mg, 1.5 mmol). The reaction mixture was stirred overnight at room temp. and the solution filtered through Celite. Then the solvent was removed in vacuo and the residue dissolved in pyridine (2 mL) containing acetic anhydride (2 mL). After the mixture had been stirred for 2 h at room temp. the solvent was removed and the residue purified by silica gel column chromatography (ethyl acetate/heptane, 25:75) to give compound **12** (367 mg, 70%) as white crystals. mp: 93−97°C (ethyl acetate/heptane). − ^1H NMR ($CDCl_3$, 300 MHz): δ = 4.63 (t, *J* = 5.4 Hz, 1 H, H-1), 4.20 (d, *J* = 5.7 Hz, 1 H, H-2), 4.07 (m, 2 H, H-2′), 3.86 (d, *J* = 5.7 Hz, 1 H, H-3), 2.31 (m, 1 H, H-4), 2.01 (s, 3 H, Ac), 1.76 (m, 2 H, H-5, H-1′), 1.58 (m, 2 H, H-5′, H-1″), 1.43 (s, 9 H, Boc), 1.38 (s, 3 H, Me), 1.24 (s, 3 H, Me). − ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 171.0, 154.6, 109.8, 85.7, 79.0, 63.5, 58.2, 36.9, 35.7, 28.4, 27.4, 26.1, 23.4, 21.0. − CI-MS (*i*BuH): *m*/*z* 344 [(M + H)$^+$]. − $C_{17}H_{29}NO_6$ (343.43): calcd. C 59.47, H 8.51, N 4.08; found C 59.15, H 8.33, N 3.86.

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[1] For recent reviews see: [1a] M. T. Crimmins, *Tetrahedron* **1998**, *54*, 9229−9272. − [1b] L. Agrofoglio, E. Suhas, A. Farese, R. Condom, R. Challand, R. A. Earl, R. Guedj, *Tetrahedron* **1994**, *36*, 10611−10670. − [1c] E. De Clercq, *Nucleosides Nucleotides* **1994**, *13*, 1271−1295.

[2] [2a] K. L. Seley, S. W. Schneller, E. De Clercq, D. Rattendi, S. Lane, C. J. Bacchi, B. Korba, *Bioorg. Med. Chem.* **1998**, *6*, 797−801. − [2b] S. M. Siddiqi, X. Chen, S. W. Schneller, *Nucleosides Nucleotides* **1993**, *12*, 267−2. − [2c] A. D. Da Silva, E. S. Coimbra, J.-L. Fourrey, A. S. Machado, M. Robert-Géro, *Tetrahedron Lett.* **1993**, *34*, 6745−6748.

[3] P. Herdewijn, E. De Clercq, J. Balzarini, H. Vanderhaeghe, *J. Med. Chem.* **1985**, *28*, 550−555.

[4] [4a] . E. Lehmann, W. A. Greenberg, D. A. Liberles, C. K. Wada, P. B. Dervan, *Helv. Chim. Acta* **1997**, *80*, 2002−2022. − [4b] F. Burlina, A. Favre, L. Fourrey, J-M. Thomas, *Chem. Commun.* **1996**, 1623−1624. − [4c] M. Egli, *Angew. Chem. Int. Ed. Engl .* **1996**, *35*, 1894−1909. [4d] B. C. Froehler, D. J. Ricca, *J. Am. Chem. Soc.* **1992**, *114*, 8320−8322.

[5] F. Burlina, A. Favre, J.-L. Fourrey, M. Thomas, *Bioorg. Med. Chem. Lett.* **1997**, *7*, 247−250.

[6] F. Burlina, P. Clivio, J.-L. Fourrey, C. Riche, M. Thomas, *Tetrahedron Lett.* **1994**, *35*, 8151−8152.

[7] For recent literature regarding the applications of the corresponding *endo*-hydroxylactone in the carbocyclic nucleoside series see: H. F. Olivo, J. Yu, *J. Chem. Soc., Perkin Trans. 1* **1998**, 391−392.

[8] C. F. Palmer, R. McCague, G. Ruecroft, S. Savage, S. J. C. Taylor, C. Ries, *Tetrahedron Lett.* **1996**, *37*, 4601−4604.

[9] [9a] H. Kapeller, C. Marschner, M. Weissenbacher, H. Griengl, *Tetrahedron* **1998**, *54*, 1439−1456. − [9b] S. M. Roberts, K. A. Shoberu, *J. Chem. Soc., Perkin Trans. 1* **1992**, 2625−2632. − [9c] M. F. Jones, S. M. Roberts, *J. Chem. Soc., Perkin Trans. 1* **1988**, 2927−2932.

[10] This benzyl amide is readily obtained by opening lactone **6** in the presence of benzylamine and acetylation of the resulting product.

[11] J. M. Mellor, N. M. Smith, *J. Chem. Soc., Perkin Trans. 1* **1984**, 2927−2931.

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