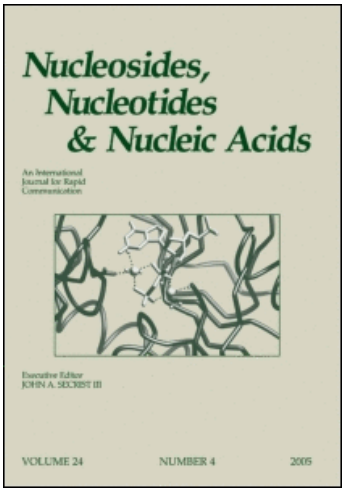

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SYNTHESIS OF CARBOCYCLIC PHOSPHONONUCLEOSIDES

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SYNTHESIS OF CARBOCYCLIC PHOSPHONONUCLEOSIDES

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ABSTRACT

Syntheses of carbocyclic analogs of phosphononucleosides are described by two different methods (introduction of the heterocycle under Mitsunobu conditions or build-up of the base around a cyclopentylamine moiety).

In case of several viruses, to be active, the nucleosides must be mono-, di- and triphosphorylated by nucleotidases or kinases enzymes. The first phosphorylation is known to be selective and limiting. To circumvent this step, pronucleotide (1,2) or nucleotide analogs, i.e. compounds in which a phosphonate group is mimicking the phosphate monoester, have been designed (3). Phosphonate analogs have also the advantage over monophosphates in that P-C bonds are not cleaved by the phosphatases which dephosphorylate monophosphates. Thus, in part of our drug discovery group, we have been investigating the syntheses of carbocyclic nucleosides (4–6), and we will report herein some carbocyclic analogues of phosphononucleosides (Fig. 1).

Considering different synthetic approaches towards the targeted compounds, we developed both convergent methods allowing the connection of the intact heterocycle moiety under Mitsunobu conditions (7), and linear methods in which the heterocycle moiety is built up around a functionalized cyclopentylamine. The

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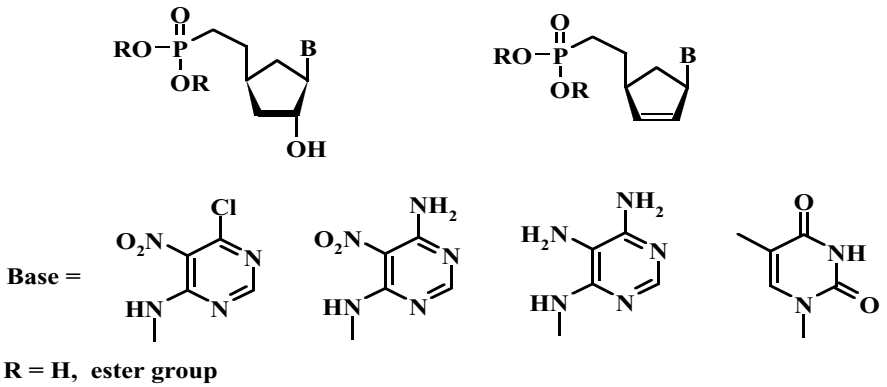
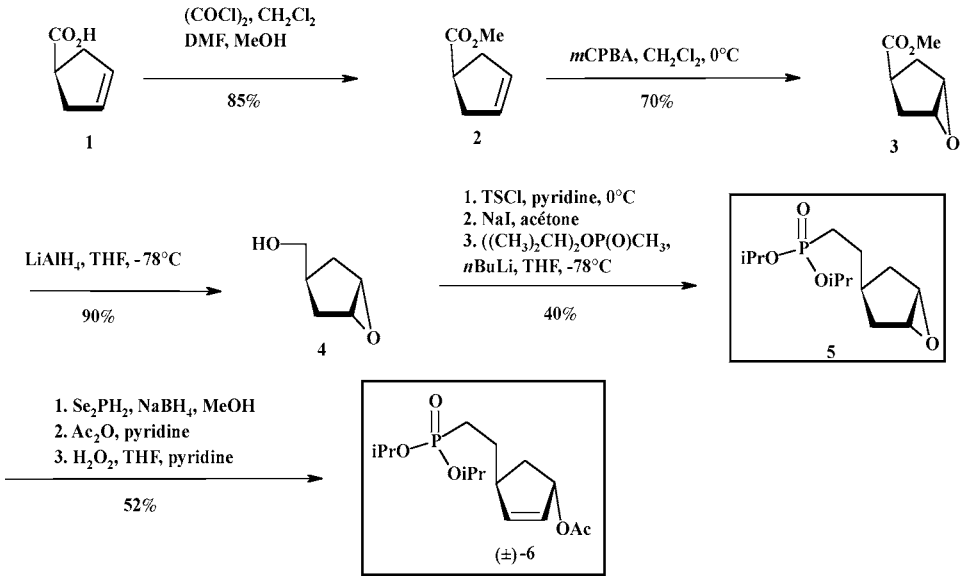


Figure 1.

requested cyclopentenyl phosphonates have been obtained from cyclopent-3-enoic acid according to Scheme 1.

The stereochemical control of the process requires that the oxirane intermediate **3** be preferentially formed on the less hindered face of the cyclopentylamine ring to direct the nucleophilic attack of the heterocycle or its precursors. Thus the epoxidation of ester **2** by MCPBA afforded a 70/30 mixture of stereoisomeric epoxides easily separated by chromatography. The only *trans*-epoxide **3** was used for the rest of the synthesis. The key synthon **5** (8) was then converted (Scheme 2) into the allylic alcohol (±)-**7** by the "selenylation-oxidation" method. Thymine



Scheme 1.

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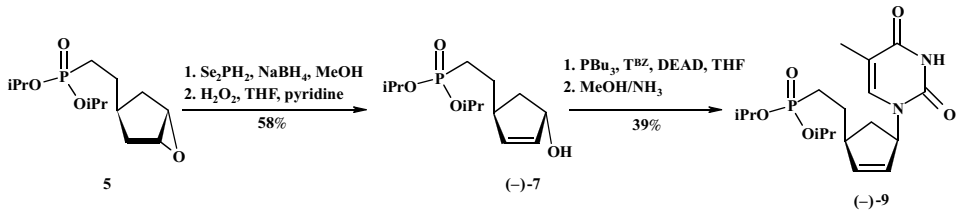
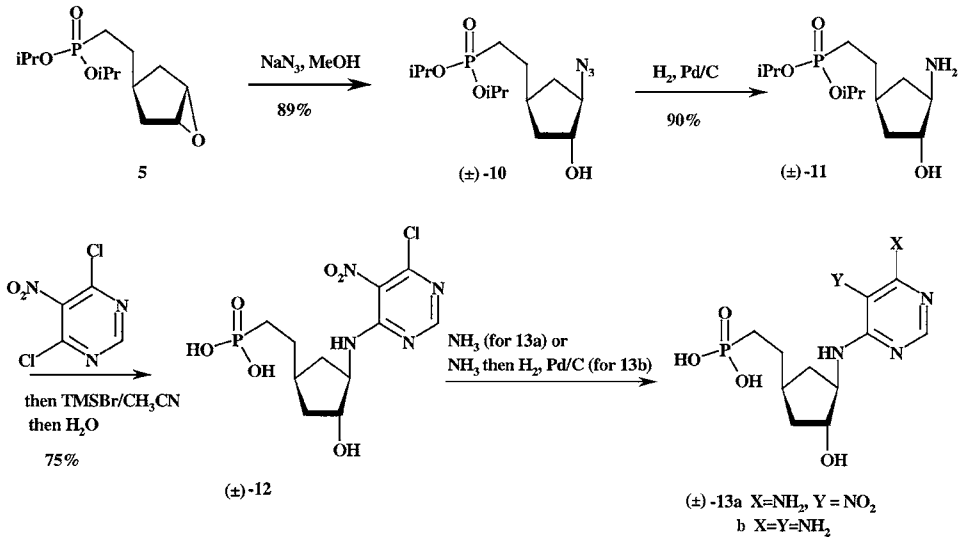


Scheme 2.



Scheme 3.

analogue (±)-**9** was successfully obtained by Mitsunobu reaction of (±)-**7** with N^3-benzoylthymine as described into Scheme 2. Compound (±)-**7** could be also obtained by deacylation of (±)-**6**.

The linear approach as depicted in Scheme 3 was used to reach other carbocyclic phosphononucleosides with an exocyclic aminopyrimidine moiety.

Thus, the *meso*-epoxide **5** after treatment with NaN_3 was converted into (±)-**10**, which was reduced by hydrogenation to provide the cyclopentylamine (±)-**11**. The amine (±)-**11** was coupled with 4,6-dichloro-5-nitropyrimidine to afford after deprotection the phosphononucleoside (±)-**12** (10). Reaction of the aromatic chlorine with methanolic ammonia gave (±)-**13a**, while hydrogenation of (±)-**13a** afforded (±)-**13b** as a new exocyclic amino carbocyclic analogue of a phosphononucleoside.

In summary, several syntheses of these hitherto unknown carbocyclic phosphononucleosides have been accomplished (11). Biological evaluations of those compounds for antiviral activity are in progress.

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9. Physico-chemical data for (±)-2″-[1′-(1-thyminyl)cyclopent-2′-enyl]ethyl phosphonic acid diisopropyl ester, (±)-9: ^{1}H-NMR ($CDCl_3$) δ 8.49 (s, 1H, NH), 7.05 (s, 1H, H_6), 6.17 (m, 1H, $H_{2'}$), 5.76–5.71 (m, 2H, $H_{3'}$, $H_{1'}$), 4.80–4.70 (m, 2H, $2 \times CH(CH_3)_2$), 2.87–2.80 (m, 1H, $H_{4'}$), 1.98 (s, 3H, CH_3), 1.84–1.75 (m, 5H, $P\underline{CH_2}$, $PCH_2\underline{CH_2}$, $H_{5'a}$), 1.38 (d, 12H, $J = 6.2$ Hz, $2 \times (CH_3)_2CH$), 1.38–1.35 (m, 1H, $H_{5'b}$); MS $m/z = 385.50$ (M + 1).
10. Physico-chemical data for (±)-2″-(2′-hydroxy-1′-*N*-(4-chloro-5-nitro-6-aminopyrimidine)-cyclopentyl)ethylphosphonic acid, (±)-12: ^{1}H-NMR ($CDCl_3$) δ 8.1 (s, 1H, H_2), 7.9 (s, 1H, NH), 4.4 (m, 1H, $H_{1'}$), 4.2 (m, 1H, $H_{2'}$), 2.4 (m, 1H, $H_{5'b}$), 2.3 (m, 1H, $H_{4'}$), 1.9 (m, 1H, $H_{3'b}$), 1.7 (m, 3H, $H_{3'a}$, $H_{1''}$, $H_{2''}$), 1.3 (m, 1H, $H_{5a'}$); MS (ion spray) m/z 366 (M+), 368 (M + 2).
11. All synthesized products have been fully characterized by ^{1}H, ^{13}C NMR and MS.

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