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Synthesis of methylenecyclopropane analogues of antiviral nucleoside phosphonates

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Abstract—Synthesis of methylenecyclopropane analogues of nucleoside phosphonates **6a**, **6b**, **7a** and **7b** is described. Cyclopropyl phosphonate **8** was transformed in four steps to methylenecyclopropane phosphonate **16**. The latter intermediate was converted in seven steps to the key *Z*- and *E*-methylenecyclopropane alcohols **23** and **24** separated by chromatography. Selenoxide eliminations (**15**→**16** and **22**→**23**+**24**) were instrumental in the synthesis. The *Z*- and *E*-isomers **23** and **24** were transformed to bromides **25a** and **25b**, which were used for alkylation of adenine and 2-amino-6-chloropurine to give intermediates **26a**, **26b**, **26c** and **26d**. Acid hydrolysis provided the adenine and guanine analogues **6a**, **6b**, **7a** and **7b**. Phosphonates **6b** and **7b** are potent inhibitors of replication of Epstein-Barr virus (EBV).

1. Introduction

Analogues of nucleoside 5′-phosphates have been a fruitful topic of research for many years.[1–3] Phosphonate derivatives, which unlike nucleotides are chemically and enzymatically stable occupy a prominent place in this effort. Another important feature of these compounds is that they are capable of circumventing the first phosphorylation step in the activation of nucleoside analogues. This is frequently a limiting event in the phosphorylation sequence, which ultimately leads to triphosphates. One of the first groups of such analogues, which yielded biologically effective compounds are acyclic nucleoside phosphonates[1] exemplified by structures **1a** and **1b** (Chart 1). Thus, compound **1a** (adefovir) and the guanine counterpart **1b** are just two examples of potent antiviral agents from this class of analogues. Because acyclic chain of **1a** and **1b** has five rotatable bonds, limiting their number will improve the entropic factor and this may lead to new biologically active analogues. Indeed, an insertion of two methylene groups between carbons 2′ and 3′ of the guanine derivative **1b** led to furanose cis- and trans-phosphonates **2** and **3** with only three rotatable bonds. Both analogues were effective[4–6] against human cytomegalovirus (HCMV) and the trans-isomer **3** is an antitumor agent.[7–9]

Our previous investigations have shown that isosteric replacement of C–O–C grouping of antiviral drugs acyclovir **4a** (B=Gua) and ganciclovir **4b** (B=Gua) with a rigid methylenecyclopropane moiety led to a new class of nucleoside analogues **5a** and **5b** (Chart 2) effective in particular against HCMV and Epstein-Barr virus (EBV).[10–13] Therefore, it seemed possible that a similar replacement of the C–O–C function in acyclic phosphonates **1a** and **1b** (Chart 1) might provide new analogues with biological activity. Regardless of the results, the antiviral testing of these analogues will provide further insight into the structure–activity relationships of methylenecyclopropane analogues. For these reasons, we have synthesized phosphonates **6a**, **6b**, **7a** and **7b**.

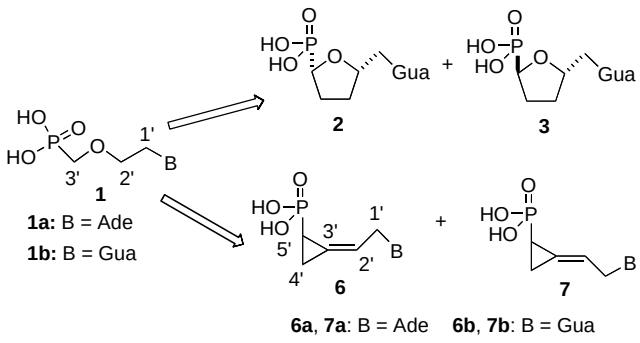

Chart 1.

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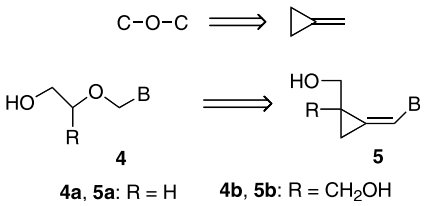


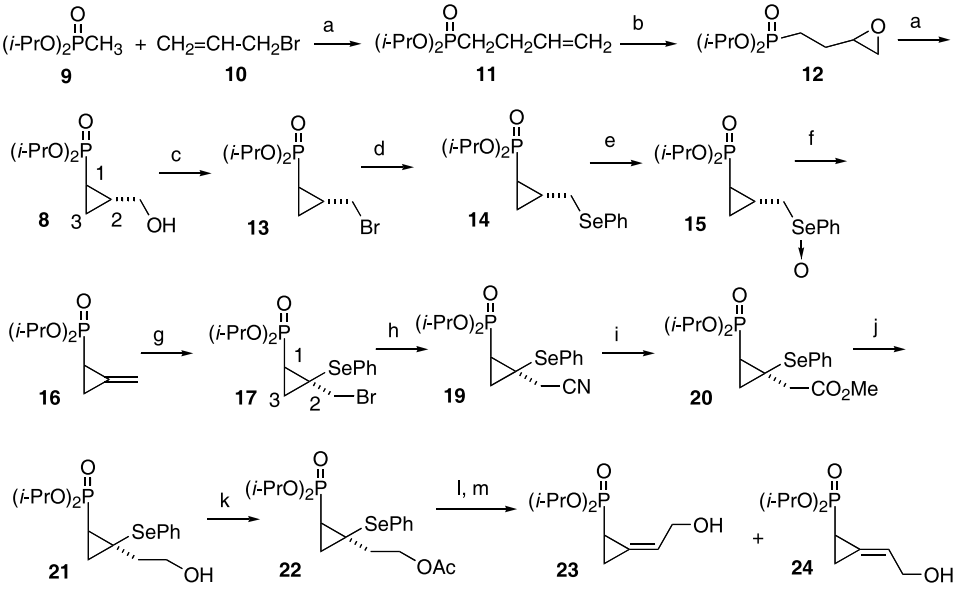
Chart 2.

2. Results and discussion

Diisopropyl (*E*)-2-hydroxymethyl-1-phosphonate[14] (**8**) was chosen as a starting material. The reproduction of the synthetic sequence on the scale of 0.27 mol was problem-free although little details were originally provided.[14] The commercially available diisopropyl methylphosphonate (**9**) and allyl bromide (**10**) were transformed to unsaturated phosphonate **11** in 70% yield (Scheme 1). Compound **11** was transformed to oxirane **12** (91%) and, finally, by an intramolecular opening of the oxirane ring to cyclopropane **8** in 80% yield. Phosphonate **8** was converted to bromo derivative **13** using Ph_3P–Br_2 reagent but the product was inseparable from the triphenylphosphine oxide formed during the reaction and, therefore, it was used as such in the next step. Reaction with PhSeNa generated from Ph_2Se_2 and $NaBH_4$ gave phenylselenenyl derivative **14** still contaminated with triphenylphosphine oxide. Although it was possible to obtain pure **14** by chromatography on a small scale, this was impractical for the intended purpose. Therefore, crude **14** was oxidized with H_2O_2 to give, after chromatography, selenoxide **15** in 76% yield after three steps (**8**→**13**→**14**→**15**). β-Elimination catalyzed by *i*-Pr_2NEt gave after a prolonged reflux in toluene (50 h) methylenecyclopropane phosphonate **16** (65%). Elimination of phenylselenoxide from cyclopropanes to give methylenecyclopropanes was reported.[15–17] Electrophilic addition of phenylselenyl bromide[18] (prepared in situ from Ph_2Se_2 and NBS) afforded intermediate **17** (88%) as a single stereoisomer as shown by NMR. It is likely that the phosphonate group of **16** directs the addition of selenium reagent to the *syn* face of double bond similar to methylenecyclopropane carboxylate function[18] to give the cis (*Z*) isomer of **17** via phenylselenonium intermediate **18** (Scheme 2).

Carbon chain extension was performed using nitrile **19**, which was obtained from **17** using Me_3SiCN and Bu_4NF method[19] in 45% yield. Methanolysis (HCl in MeOH) afforded ester **20** (72%), which was reduced with $LiBH_4$ to alcohol **21** (74%). Acetylation gave acetate **22**, which was oxidized with H_2O_2, subsequently refluxed for 24 h and then deacetylated to give the *Z*- and *E*-methylenecyclopropane phosphonates **23** and **24**. Both isomers were readily separated by chromatography to give the less polar (faster moving) *Z*-isomer **23** followed by the *E*-isomer **24** in 32 and 29% overall yield, respectively, after four steps.

Separated isomers **23** and **24** were converted to bromo derivatives **25a** and **25b** using Ph_3P and CBr_4 (67%, Scheme 3). Alkylation of adenine with **25a** or **25b** using K_2CO_3 in DMF at rt gave intermediates **26a** or **26b** in 70 and 67% yield, respectively. Hydrolysis in refluxing 6 M HCl for 20 min provided free target phosphonates **6a** (83%) and **7a** (71%). In a similar fashion, alkylation of 2-amino-6-chloropurine with bromides **25a** and **25b** afforded diisopropyl phosphonates **26c** and **26d** in 62 and 67% yield, respectively. The corresponding 7-isomers **27a** and **27b** were obtained as more polar by-products in 15% yield. Attack of the 7-position of a purine ring is a frequent



(a) BuLi, THF, −78 °C. (b) MCPBA, CH_2Cl_2. (c) Ph_3P, Br_2, CH_2Cl_2. (d) (i) $(PhSe)_2$, EtOH, (ii) NaOH, $NaBH_4$. (e) H_2O_2, THF. (f) (*i*-Pr)$_2$NEt, toluene, ². (g) $(PhSe)_2$, NBS, CH_2Cl_2. (h) Me_3SiCN, Bu_4NF, MeCN. (i) HCl (g), MeOH. (*j*) $LiBH_4$, THF. (k) Ac_2O, pyridine. (l) 1. H_2O_2, THF. 2. ². (m) K_2CO_3, MeOH/H_2O.

Scheme 1.