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The stereoselective synthesis of cyclopropylphosphonate analogs of nucleotides

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Abstract

1-Alkenylphosphonic acid derivatives of purines have been proven to exhibit significant antiviral activity among these series of compounds. Here we disclose the stereoselective synthesis of the constrained analogs of 1-alkenylphosphonate derivatives of purines via intramolecular epoxide opening reaction of γ,δ-epoxyalkanephosphonates with subsequent Mitsunobu coupling reactions with purine bases. © 1999 Elsevier Science Ltd. All rights reserved.

Since the initial report of the antiviral activity of (phosphonomethoxy)alkyl nucleotide analogs,[1a] there have been a number of investigations exploring the structure–activity relationship for this exciting class of antiviral agents, that is, nucleoside phosphonate analogs of nucleotides.[1] These investigations have led to the discovery of promising antiviral agents such as 9-[2-(phosphonomethoxy)ethyl]adenine (PMEA) and (*S*)-1-(3-hydroxy-2-phosphonomethoxypropyl)cytosine ((*S*)-HPMPC) which contain ether linkages in place of furanose rings. Recently, 1-alkenylphosphonic acid derivatives of purines, in which vinyl moiety replace furanose rings, were also proven to exhibit significant antiviral activity.

In the continuation of our study on the synthesis and properties of 1-alkenylphosphonates,[2] we were interested in the constrained analogs of these structures since it is common practice in the quest for pharmacologically active compounds to prepare conformationally constrained analogs of structures that have proven activity. Among the popular examples are 2-amino-3-phenyl-1-cyclopropane phosphonic acid,[3a] a cyclopropane analog of Phaclophen which is known as GABA antagonist, and 2-(carboxycyclopropyl)glycines[3b,c] which have been used as useful tools to investigate the physiological functions of glutamate receptors, as constrained analogs of glutamic acid. In this regard, the asymmetric synthesis of constrained forms of 1-alkenylphosphonic acid derivatives of purines presents a challenging area of research. With this in mind, we had envisaged that cyclopropylphosphonate analogs of nucleotides could be promising candidates as antiviral agents. Herein we disclose our results on the stereoselective synthesis of cyclopropylphosphonate analogs of nucleotides.

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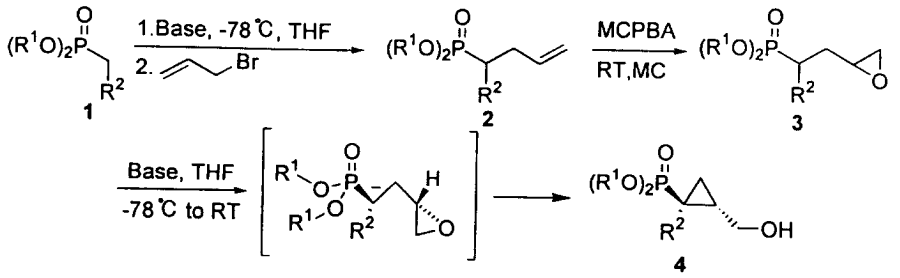
First, we gave our attention to the synthesis of hydroxy-containing cyclopropylphosphonates since the hydroxy group could be easily replaced by purine bases. Although there are some useful reports on the preparation of functionalized cyclopropylphosphonates, these methods cannot give a hydroxy group directly.[3a,4] On the other hand, the intramolecular epoxide opening reactions are known to give many kinds of hydroxy-containing carbocyclic compounds with high-yields and sometimes with good stereoselectivities.[5] To the best of our knowledge, however, there has been no report on the synthesis of the hydroxy-containing cyclopropylphosphonates by intramolecular epoxide opening reactions. Therefore, we investigated the reactivities and the stereoselectivities of the intramolecular epoxide opening reactions in organophosphonate compounds. Lithiated alkylphosphonates were allylated with allyl bromide and underwent epoxidation with MCPBA, to give γ,δ-epoxyalkylphosphonates, which were dissolved in THF and treated with a suitable base at −78°C to afford the hydroxymethylcyclopropylphosphonates via epoxide opening reaction in good yields (Scheme 1, Table 1).[6]



Scheme 1.

Except for **3f**,[7] the regiospecific epoxide opening occurred to give the cyclopropane ring exclusively without a cyclobutane ring and gave excellent stereoselectivities. The stereochemistry of the hydroxymethyl and phosphonyl groups in **4** was specifically *trans* in all cases and no products of *cis*-form were detected. In addition, the α-substituent and alkoxy group of phosphonyl moiety did not have any influence on the stereoselectivity. That the dialkylphosphoryl group is three-dimensionally more steric than α-alkyl substituent led to a *trans* compound. This stereoselectivity result was the same as that in the formation of the hydroxyalkylcyclopropylsulfones via the intramolecular epoxide opening reactions.[5b] The assignment of stereochemistry was achieved for **4c** by an NOE experiment. *trans*-Geometry was confirmed by the fact that H^{2b} showed NOE with H^4 and Ph proton, but H^{2a} did not (Fig. 1).

The stereochemistry of the others was also assigned as *trans* from the observed vicinal coupling constants J_{P-H3} of about 15 Hz.[8] The coupling constants between P and H^3 were determined by comparing the coupling pattern of H^3 in the normal condition with that in the phosphorus decoupling

Table 1
Synthesis of hydroxymethylcyclopropane phosphonates

Entry	R^1	R^2	Yields(%)[a]
a	Et	H	67
b	Et	CH_3	76
c	Et	Ph	84
d	Et	CH_2Ph	70
e	*i*-Pr	H	75
f	Et	COC_6H_4Cl	No cyclopropane[7]

[a]Isolated yields from **3**

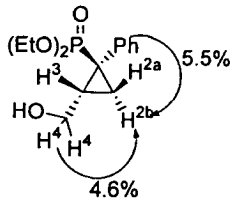
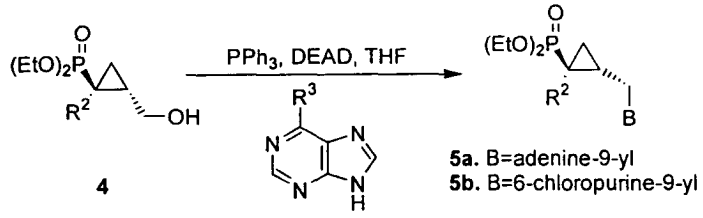


Figure 1. NOE of **4c**

condition. These data confirmed that the stereochemistry of the other products were the same *trans*-geometry.

With the hydroxymethylcyclopropylphosphonates in hand, we turned our attention to the synthesis of the target molecule via the replacement of the hydroxy group. The replacement of the hydroxy group could be achieved either by a Mitsunobu coupling reaction with purine base[9a] or by transformation to a leaving group such as the tosylate or mesylate group with subsequent substitution by purine base.[9b] We adopted the former route and it gave good results. The coupling reactions of **4a** and **4b** with 6-chloropurine and adenine under Mitsunobu reaction conditions afforded **5a** and **5b** in yields of 42% and 46%, respectively, after column chromatography (Scheme 2).[10] While the coupling of **4b** and 6-chloropurine was run at 0°C to give the product in 46% yield, the synthesis of **5a** had to be run at −10°C to avoid the unwanted coupling of the hydroxy and primary amine group. First, we adopted an indirect synthetic route to an adenine derivative. Azide substitution with subsequent hydrolysis of **5b** was attempted,[1c] but the transformation of **5b** to an adenine derivative by this route was proven to be inefficient.[11] Instead, adenine derivative **5a** could be synthesized via a clever route reported by Chen et al., direct Mitsunobu coupling of alcohol and adenine at a lower temperature.[9a]



Scheme 2.

Compounds **5** might be considered as the constrained analogs of 1-alkenylphosphonate derivatives of purines which were proven to be antivirally active agents. These are the only analogs bearing cyclopropane rings instead of the furanose rings in the nucleoside phosphonate series that have been reported to possess strong antiviral activity.[12] The synthesis and the biological evaluation of the various structures of this series are under progress and will be reported in due course.

In summary, we have devised an efficient and stereoselective synthetic route to hydroxymethyl-cyclopropylphosphonates in good yields, which are versatile reagents as functionalized cyclopropyl-phosphonates. Then these compounds were transformed into novel cyclopropylphosphonate analogs of nucleotides that are expected to have a good biological property.

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6. Preparative procedure for **4c**: To a stirred solution of **3c** (79 mg, 0.29 mmol) was added LDA (0.4 mmol, 2 M solution in THF. For the epoxide opening of **3a**,**b**,**c**, and **e**, *n*-BuLi was used, while LDA for **3d** in consideration of the pK_a of benzyl-α-proton) at −78°C under nitrogen atmosphere. After being stirred for 1 h at −78°C the mixture was allowed to warm to room temperature. After stirring for 1 h at room temperature, the reaction mixture was quenched with NH_4Cl and extracted with diethyl ether. The combined organic layer was dried with $MgSO_4$, and the solvent was removed in vacuo. The product was purified by column chromatography to give **4c**. Eluent, ethyl acetate:acetone (4:1). ^1H NMR (300MHz, $CDCl_3$): δ 7.37–7.34 (m, 2H), 7.26–7.18 (m, 5H), 4.01–3.87 (m, 4H), 3.30–3.17 (m, 2H), 3.06 (br s, 1H), 1.97–1.91 (m, 1H), 1.65–1.55 (m, 1H), 1.21–1.12 (m, 6H), 1.06–0.99 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.34, 131.47 (d, *J*=4.05), 128.10 (d, *J*=2.22), 127.27 (d, *J*=2.63), 62.3 (dd, *J*=14.55, 6.6), 62.07 (d, *J*=1.88), 26.00 (d, *J*=186.83), 24.05 (d, *J*=2.25), 16.18 (d, *J*=6.08), 14.46 (d, *J*=2.93); HRMS, calcd for $C_{14}H_{21}O_4P$: 284.1177; found: 284.1175.
7. The reaction of **2f** and MCPBA yielded **3f**, but it was spontaneously cyclized to give 2-hydroxymethyl-4-phosphonyl-5-(4-chlorophenyl)-2,3-dihydrofuran by action of sodium bicarbonate which was added in the work-up step to remove unreacted MCPBA.
8. J_{PH}s of cyclopropylphosphonates in *trans*-geometry are known to be 14.5 to 20 Hz. (a) Benezra, C. *J. Am. Chem. Soc.* **1973**, *95*, 6890. (b) Mass, G. *Phosphorus and Sulfur* **1983**, *14*, 143. (c) Jubalt, P.; Goumain, S.; Feasson, C.; Collignon, N. *Tetrahedron* **1998**, *54*, 14767.

Coupling constants between P and H^3

Entry	4a	4b	4c	4d	4e
$J_{P\text{-}H3}$ / Hz	14.95	16.73	16.53	16.11	15.49

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10. A mixture of **4a** (166 mg, 0.80 mmol), 6-chloropurine (150 mg, 0.97 mmol), and triphenylphosphine (505 mg, 1.93 mmol) in anhydrous THF, cooled to −10°C, was treated with diethyl azodicarboxylate (280 mg, 1.59 mmol). After the mixture was stirred at ambient temperature for 10 h, the solvent was removed and the residue was purified by column chromatography on silica gel using acetone as eluent to give **5a** (109 mg, 0.34 mmol). ^1H NMR (300 MHz, $CDCl_3$): δ 8.27 (s, 1H), 7.87 (s, 1H), 4.25 (ddd, 1H, *J*=14.45, 6.23, 2.07), 4.00–3.92 (m, 3H), 3.87–3.66 (m, 2H), 1.81–1.77 (m, 1H), 1.23–1.00 (m, 6H), 0.99–0.93 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.70, 152.92, 149.90, 139.68, 61.86 (dd, *J*=11.10, 6.08), 46.52 (d, 3.75), 17.14 (d, *J*=3.90), 16.20 (dd, *J*=11.63, 6.08), 12.00, 9.37 (dd, *J*=11.18, 4.80); HRMS, calcd for $C_{13}H_{20}N_5O_3P$: 325.1304; found: 325.1301.
11. A couple of the attempted azide substitutions of **5b** led to the formation of two inseparable mixtures, including an azide-substituted product.
12. A few related examples describe the nucleotide analogs bearing a cyclopropane ring just as a pendant, not as a replacement of the furanose ring. Yu, K.-L.; Bronson, J. J.; Yang, H.; Patick, A.; Alam, M.; Brankovan, V.; Datema, R.; Hitchcock, M. J. M.; Martin, J. C. *J. Med. Chem.* **1993**, *36*, 2726.