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The first synthesis of enantiomerically pure cyclopropylphosphonate analogues of nucleotides via asymmetric cyclopropanation of chiral (1-diethoxyphosphoryl)vinyl *p*-tolyl sulfoxide

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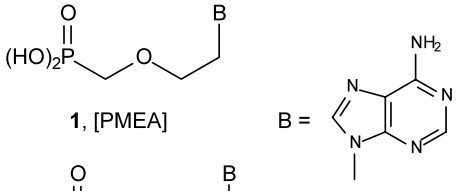
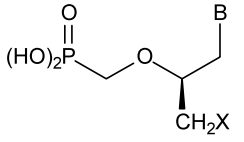
Abstract—(*S*)-(+)-(1-Diethoxyphosphoryl)vinyl *p*-tolyl sulfoxide undergoes cyclopropanation with ethyl (dimethylsulfuranylidene)acetate (EDSA) in a highly diastereoselective manner (facial stereoselectivity up to 12:1). The major diastereomer obtained in this reaction, (1*S*,2*S*)-(1-diethoxyphosphoryl-2-ethoxycarbonyl)cyclopropyl *p*-tolyl sulfoxide, was converted in three steps into enantiopure cyclopropylphosphonate analogues of purine nucleotides as the constrained forms of antiviral 1-alkenylphosphonic acid derivatives of purines.

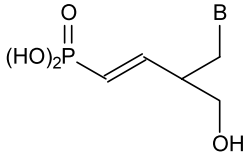
The discovery of novel nucleosides and nucleotides as antiviral and anticancer agents has been the goal of research of chemists for several decades.[1] It has been shown that replacement of the furanose ring of a nucleotide with an acyclic side chain as well as substitution of the $POCH_2$ moiety of the monophosphate for the bioisostere, PCH_2O, resulting in a substantial simplification of the structure, led in many cases to new antiviral agents of significant therapeutic potency. In this way, for example, adefovir **1**,[2,3] tenofovir **2**[4,5] and cidofovir **3**,[6] a unique class of acyclic nucleotide analogues, were invented and are currently being clinically utilized or investigated as antiviral therapeutics.



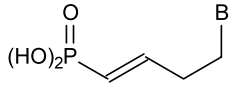


2, X=H, [(*R*)-PMPA]
3, X=OH, [(*S*)-HPMPA]

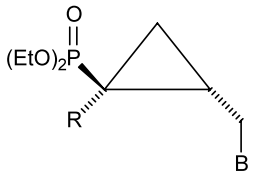
Recently, acyclic nucleotide analogues incorporating the alkenylphosphonic acid group as a phospho-sugar mimic appeared to have great potential for being effective antiviral agents.[7] Thus, for example, (*E*)-9-[2-hydroxymethyl)-4-phosphonobut-3-enyl]adenine **4** showed selective antiherpes virus activity while the structurally related compound **5** displayed selective antiretrovirus activity.



4, B=adenin-9-yl



5, B=2,6-diaminopurin-9-yl



6a, R=H, B=adenin-9-yl
6b, R=H, B=6-chloropurin-9-yl
7, R=Me, B=6-chloropurin-9-yl

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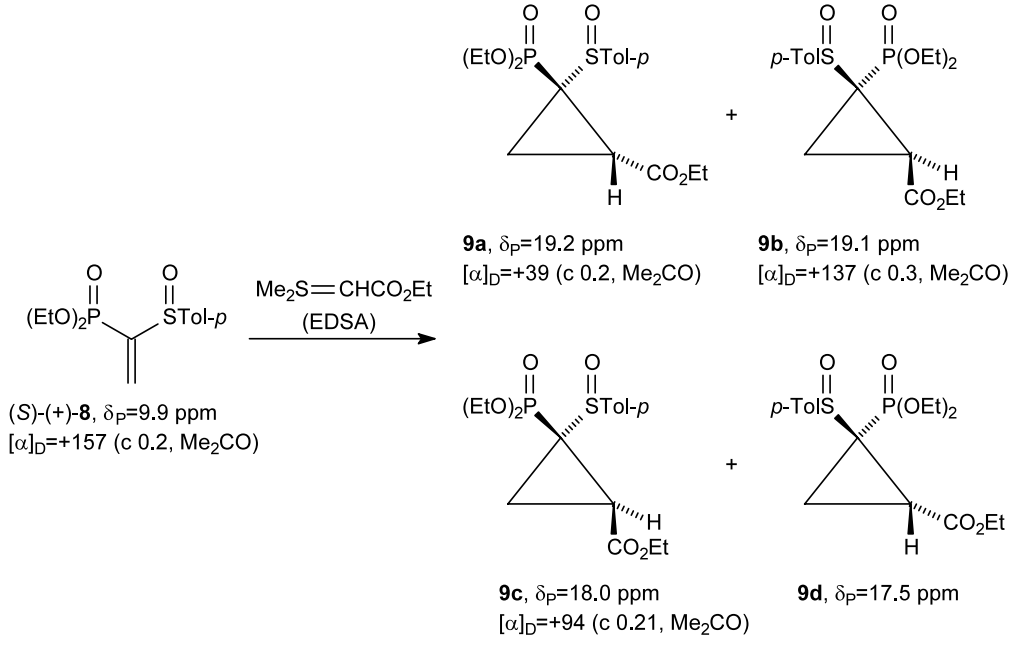
Since the design and synthesis of conformationally constrained analogues of bioactive compounds has recently been an important strategy in modern drug discovery, we turned our attention to cyclopropylphosphonate analogues of nucleotides which may be considered as the constrained forms of 1-alkenylphosphonic acid derivatives of purines. Having this in mind, Oh et al.[8] described in 1999 the synthesis of 9-[2-(3-diethoxyphosphorylcyclopropyl)methyl]adenine **6a** and 6-chloropurine analogue **7** involving in a key step, intramolecular epoxide opening reaction of γ,δ-epoxyalkanephosphonates. However, this elegant method only allowed them to obtain these potential antiviral compounds in racemic form. As in the case of other classes of chiral bioactive compounds, the biological activity of these cyclopropylphosphonate analogues of nucleotides should be dependent on the absolute configuration of the cyclopropyl stereogenic centre. Therefore, we decided to develop a new approach to the synthesis of **6** enabling their preparation in enantiopure form. Encouraged by our results on the asymmetric synthesis of aminophosphonic acids[9] and asymmetric cyclopropanation[10] mediated by a chiral sulfinyl auxiliary we based our method upon the cyclopropanation reaction of (*S*)-(+)-(1-diethoxyphosphoryl)vinyl *p*-tolyl sulfoxide **8**[11] with ethyl (dimethylsulfuranylidene)acetate (EDSA). It was found that the stereochemical outcome of this reaction was strongly dependent on the nature of the ylide component. Thus, when CH_2Cl_2 solution of the sulfoxide **8** was treated at room temperature with the freshly and separately prepared EDSA,[12] the cyclopropanation product **9** was obtained in 70% yield as a mixture of four diastereomers **9a**–**d** in a 12:2:7:1 ratio. However, the reaction of **8** with EDSA generated in situ from dimethyl(ethoxycarbonylmethyl)sulfonium bromide in the presence of DBU in toluene afforded in high yield (95%) the diastereomeric cyclopropanes **9a**–**d** in a 36:3:12:1 ratio. The same reaction carried out in methylene chloride gave **9a**–**d** in a 13:2.7:8:1 ratio. Three dominant diastereomers, **9a**–**c**, were isolated by column chromatography on silica gel and fully characterized (^{1}H, ^{13}C and ^{31}P NMR, HRMS; for some selected data see Schemes 1 and 2).

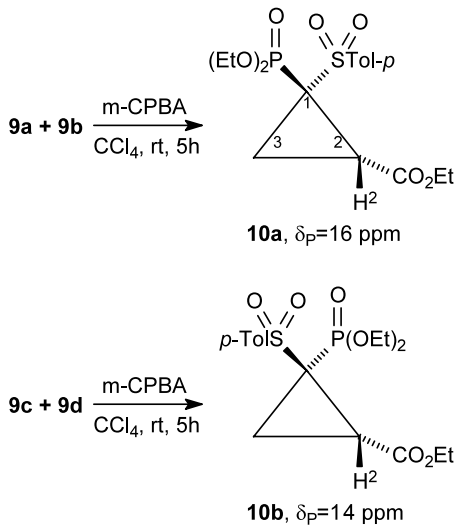
Analysis of the ^{1}H and ^{13}C NMR spectra of **9a**–**c** revealed that the coupling constant values, $^3J_{HP}$ and $^3J_{CP}$, which are usually conclusive for the assigment of the *cis*–*trans* geometry in substituted cyclopropylphosphonates,[13] do not differ significantly thus precluding firm establishment of the relative configuration of the diastereomeric cyclopropyl sulfoxides under discussion. To overcome this problem, two pairs of the cyclopropyl sulfoxides **9**, namely **9a**+**9b** and **9c**+**9d**, were oxidized to the corresponding sulfones **10** by *meta*-chloroperbenzoic acid. The results are summarized in Scheme 2.

It turned out that in the case of the sulfones **10a** and **10b** the relevant coupling constants showed greater differences (Scheme 2) and allowed the assignment of their relative configurations. Hence, the sulfone **10a** has the *cis*-geometry whereas **10b** is the *trans*-isomer. Consequently, the stereochemistry of the first pair of the cyclopropyl sulfoxides was assigned as *cis* and of the second one as *trans*.

The stereochemical course and outcome of the cyclopropanation reaction can be best explained in terms of the transition state model for cyclopropanation of α-phosphorylvinyl sulfoxides put forward by us earlier[10a] in which the approach of EDSA to the carbon–carbon double bond in (*S*)-(+)-**8** takes place preferentially from



Scheme 1.



Coupling constants between P and H^2 and C(O) in sulfoxides **9** and sulfones **10**

Compound	$^3J_{P-H}$ (Hz)	$^3J_{P-C}$ (Hz)
9a	15.8	3.3
9c	14.9	4.5
10a	14.7	3.1
10b	9.5	5.4

Scheme 2.

the less hindered diastereotopic face occupied by the lone electron pair of sulfur (top-face attack, Fig. 1). Therefore, the two major diastereomers **9a** and **9c** formed have the same configuration at the carbon atom C(1) and opposite at C(2) bearing the ester group. Moreover, based on this model it is possible to tentatively assign the absolute stereochemistry to the cyclopropyl ring in **9a** and **9c** as (1*S*,2*S*) and (1*S*,2*R*), respectively. Consequently, the absolute configuration ascribed to the cyclopropyl ring in the minor diastereomers **9b** and **9d**, which are formed by the bottom-face attack, is (1*R*,2*R*) and (1*R*,2*S*).

Since our goal was to find a convenient procedure for the preparation of enantiopure cyclopropylphosphonate analogues of nucleotides **6**, the cyclopropyl sulfoxide **9a** was treated with five equivalents of methylmagnesium iodide at ca. −30°C to give the cyclopropyl phosphonate (−)-**11a** as a single diastereomer having the *trans*-geometry as indicated by a small vicinal coupling constant between phosphorus and carbonyl carbon, $^3J_{CP}=4.4$ Hz. However, treatment of **9c** with MeMgI under the same conditions gave a mixture of (+)-**11a** and (+)-**11b**[14] in a 4:1 ratio which was separated by column chromatography (Scheme 3). There is no doubt that the formation of (+)-**11a** in this reaction is due to inversion of the configuration at C(1) and thermodynamic control affording a more stable *trans*-isomer as the major product.

In the next step of the synthesis of our targets, the ethoxycarbonyl group in (−)-**11a** was reduced to the hydroxymethyl group using lithium borohydride and one equivalent of methanol. Finally, the reduction product (−)-**12** was coupled with adenine and chloropurine under the Mitsunobu reaction conditions (triphenylphosphine, diisopropylazidodicarboxylate, DIAD) affording the desired compounds (−)-**6a** and (−)-**6b** in moderate yields (see Scheme 4).

In summary, we have developed an easy synthesis of enantiopure cyclopropylphosphonate analogues of purine nucleotides **6** involving in a key step asymmetric cyclopropanation of chiral α-phosphorylvinyl *p*-tolyl sulfoxide with ethyl (dimethylsulfuranylidene)acetate (EDSA). The synthesis of other optically active isomers of **6** and evaluation of antiviral properties are currently being studied in our laboratory.

Acknowledgements

Financial support by the State Committee for Scientific Research (Grant No Z-005/T09/99) is gratefully acknowledged.

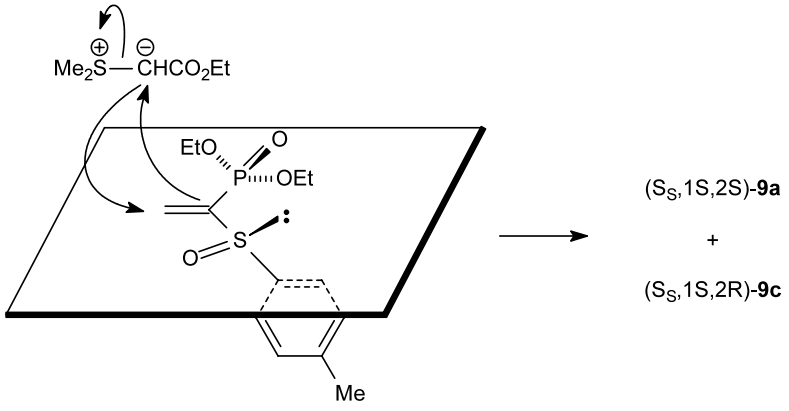
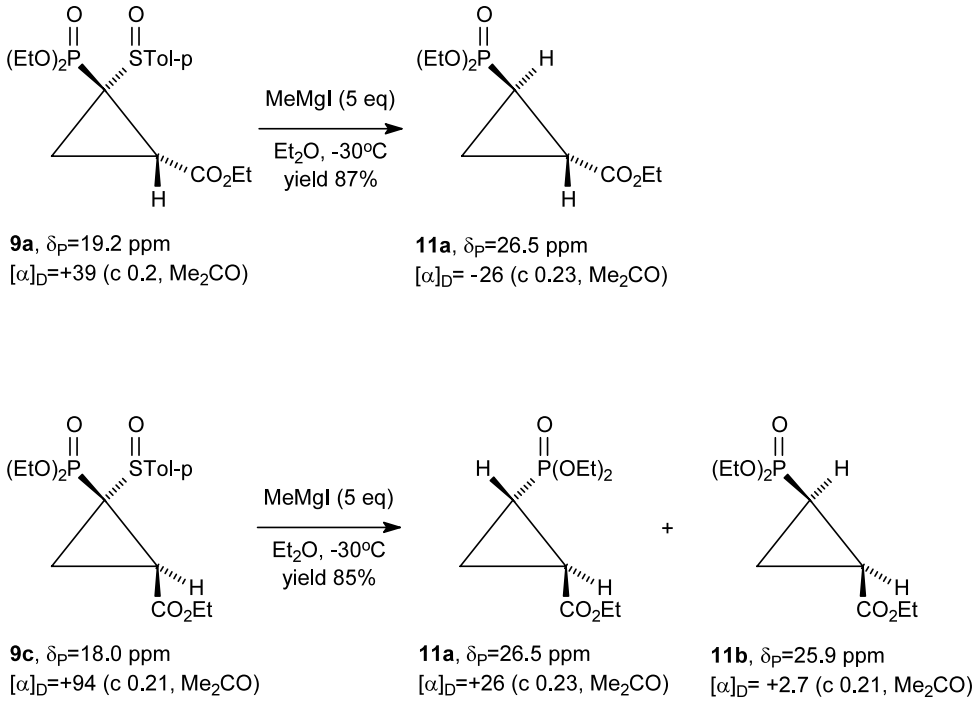


Figure 1. The preferred steric course of the reaction of EDSA with (*S*)-(+)-**8**.



9a, δ_P=19.2 ppm
$[\alpha]_D$=+39 (c 0.2, Me_2CO)

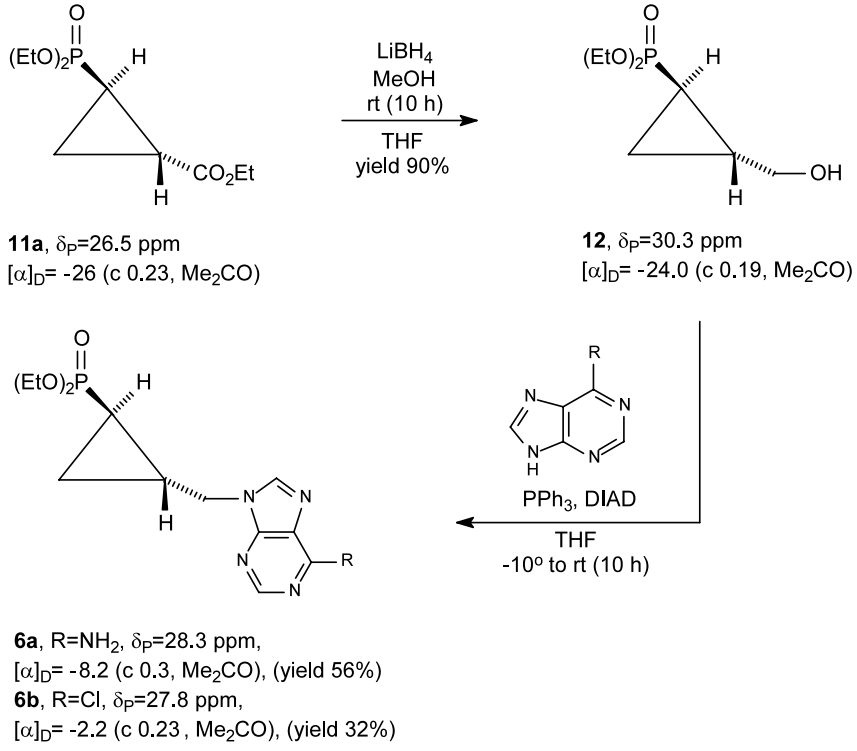
11a, δ_P=26.5 ppm
$[\alpha]_D$= -26 (c 0.23, Me_2CO)

9c, δ_P=18.0 ppm
$[\alpha]_D$=+94 (c 0.21, Me_2CO)

11a, δ_P=26.5 ppm
$[\alpha]_D$=+26 (c 0.23, Me_2CO)

11b, δ_P=25.9 ppm
$[\alpha]_D$= +2.7 (c 0.21, Me_2CO)

Scheme 3.



11a, δ_P=26.5 ppm
$[\alpha]_D$= -26 (c 0.23, Me_2CO)

12, δ_P=30.3 ppm
$[\alpha]_D$= -24.0 (c 0.19, Me_2CO)

6a, R=NH_2, δ_P=28.3 ppm,
$[\alpha]_D$= -8.2 (c 0.3, Me_2CO), (yield 56%)
6b, R=Cl, δ_P=27.8 ppm,
$[\alpha]_D$= -2.2 (c 0.23 , Me_2CO), (yield 32%)

Scheme 4.

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14. The value of $^{3}J_{CP}$ in (+)-**11b** equal to 12 Hz confirms the *cis*-relationship of the phosphoryl and ester groups.