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Synthesis of novel deoxy λ^5 phospha sugar nucleosides: 1,3-dipolar cycloaddition of an azidophospholane with alkynes

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Abstract

Several novel phospha sugar nucleosides, analogs of normal sugar nucleosides, were synthesized from a phospholene 1-oxide derivative. Bromination of a phospholene precursor in aqueous organic medium gave regio diastereomers, the *threo* and *erythro* bromohydrins **3** (1-bromo-1,3,4-trideoxy-1,4-*C*-[(*R*,*S*)-phenylphosphinylidene]-*glycero*-tetrofuranose). Further substitution of the *threo* isomer **3a** with sodium azide led to its corresponding azidophospholane **4** (1-azido-1,3,4-trideoxy-2-methyl-1,4-*C*-[(*R*)-phenylphosphinylidene]-β-D-*glycero*-tetrofuranose). 1,3-Dipolar cycloaddition of **4** with various electron-deficient and electron-rich alkynes afforded triazole derivatives that are nucleoside analogues. The strong electron-withdrawing phosphoryl group in the hemiacetal ring exerted no effect over reaction regioselectivity of the 1,3-dipolar cycloaddition, but steric effects of the alkynes played a vital role on the selectivity, since the regioisomer ratios and the rates and yields of cycloadducts changed as the bulkiness of the substituents on the acetylene changes. Structures of all compounds were unequivocally confirmed by ^{1}H, ^{13}C, and ^{31}P NMR and mass spectral studies. Single crystal X-ray crystallographic analysis of some derivatives allowed determination of configuration of the phospha sugar nucleosides.

Keywords: Phospha sugars; Hetero sugars; Nucleoside analogues, Bromohydrins; 2-Azidophospholane; 1,3-Dipolar cycloaddition, X-ray crystallography, Absolute configuration

1. Introduction

Sugars having other atoms replacing the ring oxygen are inherent and interesting substances because of their wide range of potential biological activities in living systems. The potential bioactivity of natural, as well as synthetic nucleoside analogues has prompted the synthesis of analogues and explore their possible use as anti-HIV, and anti-cancer agents.[1–3] In searches for therapeutically improved inhibitors of HIV, a wide variety of sugar-modified nucleosides have been developed and found to possess potential bioactivity. Among them, Ribavirin,[4] AZT,[5] 4′-thio-ddC,[6] Aristeromycin,[7] and others (Scheme 1) are the most interesting, because of their potent anti-HIV activities. Recent developments have indicated that functional changes of the sugar moiety may lead to potent bioactivity.[8] Replacement of hemiacetal

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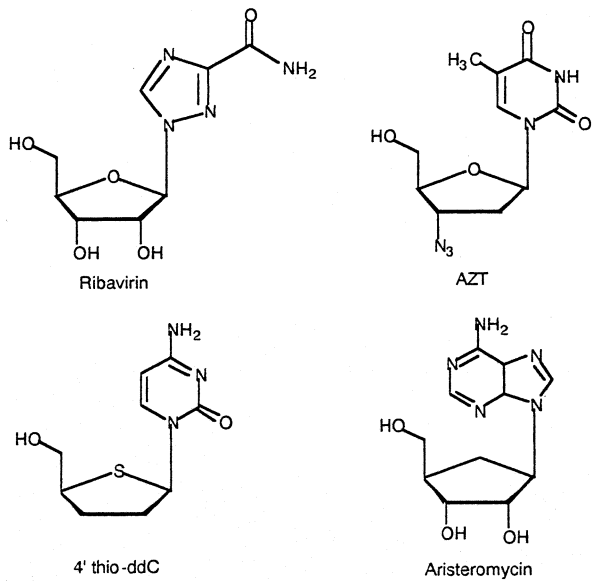


Scheme 1.

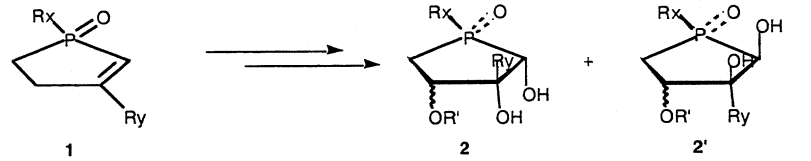
ring oxygen with methylene, nitrogen, or sulfur is one approach for making functional changes in the nucleoside subunits.[8,9] Several bioactive sugar-modified glycosides and nucleosides in which the hemiacetal ring oxygen is replaced by methylene, sulfur, or nitrogen have also been isolated from natural sources.[2] Several novel classes of heterosugars such as *carba*,[10] *aza*,[11] and *thia sugar*[12] nucleosides been studied extensively. Our interest was that of synthesis of phosphafuranose nucleoside analogues, in which the oxygen of the hemiacetal ring is replaced by phosphorus.‡

Despite extensive studies on the synthesis, spectral, and bioactivity of such 'pseudo sugars' as *carba*, *aza*, and *thia sugars*, little research has been done on phospha sugars, particularly on phospha sugar nucleosides and glycosides, as they have not been found in natural sources. Considerable recent attention has been focused on the synthesis and bioactivity of simple phospha sugar analogues,[13] but not on phospha sugar nucleosides. Riley[14] and co-workers reported some ribavirin analogues of nucleosides containing phosphorus in the nucleoside base subunit, but not in the sugar subunit. Synthesis of phospha sugars is rather difficult due to long reaction sequences and low yields,[15] and preparations generally use normal sugars as starting materials.[16,17] We wished to develop a more general route to such phospha sugars as **2** and have reported the synthesis of tetrofuranose analogs[18] using phospholenes (Scheme 2) as potential starting materials.[19] Our interest to develop potential inhibitors of HIV led us to synthesize phospha sugar nucleosides containing a triazole ring, report here the synthesis of a key intermediate 2-azidophospholane and its 1,3-dipolar cycloaddition reactions with various electron-rich and electron-deficient alkynes.[20]

2. Results and discussion

Our primary aim was to develop a general route for the synthesis of phospha sugar nucleosides from non sugar starting materials. To prepare the desired triazole derivatives **6**–**15**, of phospha sugar nucleosides, we started from 3-methyl-1-phenyl-2-phospholene 1-oxide (**1a**) because introduction of the azido group at 2-position was expected to be relatively easy through its 2-bromophospholane derivative **3**.[21] Bromination of 2-phospholene **1a** in an aqueous organic medium afforded 2-bromo-3-hydroxyphospholane diastereo-

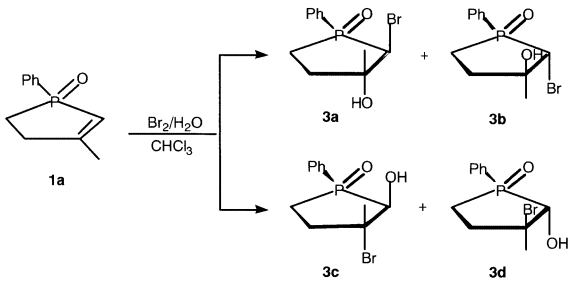
‡ The term 'phospha' strictly denotes replacement of a carbon atom in the parent structure by phosphorus (see 2-Carb-34.1).



1a: Rx = Ph, Ry= Me
1b: Rx = Ph, Ry= H
1c: Rx = OMe, Ry= Me
1d: Rx = OMe, Ry= H
1e: Rx = OEt, Ry= Me
1f :Rx = OEt, Ry= H

2a ;**2'a** : Rx = Ph, Ry=Me, R'= COMe
2b ;**2'b** : Rx = Ph, Ry=H, R'= COMe
2c ;**2'c** : Rx = OMe, Ry=Me, R'= COMe or COPh
2d ;**2'd** : Rx = OMe, Ry= H, R'= COMe
2e ;**2'e** : Rx = OEt, Ry=H, R'= COMe or COPh
2f ; **2'f**: Rx = OEt, Ry= Me, R'= COMe or COPh

Scheme 2.

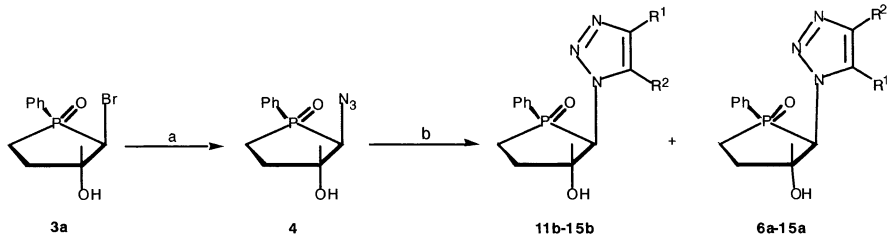


Scheme 3.

mers **3a** (*threo*) and **3b** (*erythro*), in addition to the minor regiodiastereomers, *threo*-3-bromo-2-hydroxyphospholane 1-oxide (**3c**) and the erythro isomer **3d** (Scheme 3). Preliminary TLC analysis of the reaction mixture shows only two spots, suggesting formation of two major isomers, **3a** and **3b**, and **3a** (1-bromo-1,3,4-trideoxy-1,4-*C*-[(*R*,*S*)-phenylphosphinylidene]-*glycero*-tetrofuranose) was separated by fractional crystallization from chloroform and *n*-hexane. Detailed spectral analysis of the **3b** fraction revealed that the presence of the minor regiodiastereomers **3c** (*threo*) and **3d** (*erythro*), but attempts to separate **3c** and **3d** from **3b** were unsuccessful, and hence the isomer ratios were determined by ^{31}P NMR spectroscopy. The isomer ratios of **3a**, **3b**, **3c,** and **3d** are 4:2:1:1, respectively. In contrast, bromination of a 3-unsubstituted-2-phospholene, 1-phenyl-2-phospholene, 1-oxide (**1b**) under similar conditions gave only threo and erythro 2-bromo-3-hydroxy-1-phenylphospholane 1-oxides (homologs of **3a** and **3b**) in 2:1 ratio with no indication of regiodiastereomers homologous with **3c** and **3d**.[21] This difference is explicable by the involvement of a cyclic bromonium ion intermediate. Such a cyclic bromonium ion intermediate formed between bromine and the phospholene may be destabilized by the presence of the electron-donating methyl group and the strongly electron-withdrawing P=O group on each side of the alkene. Therefore, the equilibrium of a π complex with bromine may be altered and the nucleophilic, OH^- group could attack at C-2 to give isomers **3c** and **3d**.

The azidophospholane intermediate **4** was readily prepared from *threo*-2-bromo-3-methyl-1-phenylphospholane 1-oxide (**3a**) in reasonably good yield (87%). Treatment of **3a** with sodium azide in *N*,*N*′-dimethylformamide (DMF) at 70 °C for 24 h gave 1-azido-1,3,4-trideoxy-2-methyl-1,4-*C*-[(*R*)-phenylphosphinylidene]-β-D-*glycero*-tetrofuranose (**4**) in 87% yield. In the conversion of compound **3a** to **4**, the retention of configuration was observed at C-2 where bromine was substituted by the azido group. The retention of configuration at C-2 via a double inversion presumably involves formation of an epoxide intermediate.[22] This is supported by the δ values and as $^2J_{P,H}$ coupling constants for H-2. The ^{1}H NMR spectra of compounds **3a** and **4** exhibited doublets at δ 4.20 and 4.00 with coupling constants, $^2J_{P,H}$, of 4.0 and 2.0 Hz, respectively, indicating a similar arrangement of H-2 in both compounds. Several unexplained failures were observed when attempted to convert the mixture of **3b**, **3c**, and **3d** into their corresponding azides under similar conditions. The azide **4** permitted the synthesis of a large number of nucleoside analogues of phospha sugars via 1,3-dipolar cycloaddition with various alkynes **5** in a single step reaction (Scheme 4).

1,3-Dipolar cycloaddition of **4** with mono- and disubstituted alkynes **5a**–**5j** containing electron-donating and electron-withdrawing groups, proceeded in good yields (Table 1) in 1,2-dimethoxyethane (DME) at reflux temperature. As expected, the reaction of monosubstituted alkynes **5f**–**5j** gave two regioisomers, 4′- and 5′-substituted triazole derivatives **a** and **b**, whose chromatographical and spectroscopical properties were markedly different, permitting easy separation and unequivocal structural assignment of both regioisomers. The regioisomers **a** and **b** were separated by silica gel column chromatography using 10:1 $CHCl_3$–MeOH as the eluent. Interestingly, analysis of the reaction product of (trimethylsilyl)acetylene (**5e**) with azide **4** revealed only one isomer, **10a**, in contrast to the adducts of other monosubstituted alkynes. The results (Table 1) show that the rate of reaction of more electron-deficient dipolarophiles with azide **4** is faster than those of less electron-deficient or electron-rich dipolarophiles. Even though the phosphoryl group in the hemiacetal ring of the phospha sugar is a strongly electron-withdrawing group, little effect was exerted over the dipolar cycloaddition



Scheme 4. (a) NaN_3, DMF, 70 °C, 24 h; (b) substituted acetylenes (**5**), DME, reflux.

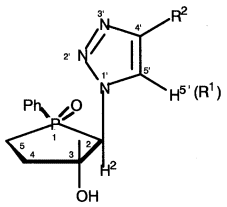
Table 1
1,3-Dipolar cycloaddition of azide **4** with various substituted alkynes **5a–j**

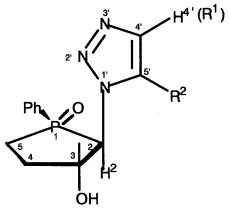
Alkyne	R′	R^2	Reaction time (h)	Product	Yields (%)	Mp (°C)
5a	CO_2Me	CO_2Me	12	**6a**	79	205–706
5b	CO_2Et	CO_2Et	16	**7a**	84	175–176
5c	CH_2OH	CH_2OH	75	**8a**	68	205–206
5d	CO_2H	CO_2H	24	**9a**	79	175–176
5e	H	$SiMe_3$	24	**10a**	57	221–222
5f	H	CH_2OH	48	**11a**	36	184–185
			48	**11b**	38	227–228
5g	H	CMe_2OH	120	**12a**	42	204–205
			120	**12b**	25	215–216
5h	H	CO_2Me	12	**13a**	49	206–207
			12	**13b**	37	219–220
5i	H	Ph	96	**14a**	33	230–232
			96	**14b**	17	228–229
5j	H	CMe_3	36	**15a**	55	224–227
			36	**15b**	21	247–250

conditions and also on the ratio of regioisomers, since the obtained results were very similar to those of other reported cycloaddition reactions.[23,24] The steric effects of substituents on the acetylene played a major role on the regioisomer ratios, since the reaction of propargyl alcohol (**5f**) with azide **4** afforded regioisomers **11a** and **11b** in 1:1 ratio, whereas (trimethylsilyl)acetylene (**5e**) gave only one isomer, the 4′-trimethylsilyl derivative **10a**. This type of dominating effect on regioselectivity by the trimethylsilyl group has been observed in the cycloaddition reactions of diazoalkenes[25,26] and also *N*-(azidomethyl)-benzisothiazoles.[24] The steric effect of the trimethylsilyl group is more dominant in regioselectivity than the electronic effect of substituents, because of the high ability of silicon to stabilize the transition state.[24]

The structure of products **6a–15a** and **11b–15b** were confirmed by their analytical and spectral (^1H, ^{13}C and ^{31}P NMR and mass) data. The orientation of the P=O group of the phospholane ring in compounds **6–15** was established from the chemical shifts of H-2 and the $^2J_{P,H}$ coupling constants (Table 2). The downfield shift of H-2 and its larger $^2J_{P,H}$ coupling constant suggests the *cis* (or gauche) relationship of H-2–C-2–P=O.[27] Interestingly the H-2 proton resonated as a doublet of doublets indicating long-range coupling between H-2 and H-4e, which was also confirmed by homospin decoupling studies. The smaller coupling constants (1.6–2.1 Hz) were attributed to long-range couplings $^4J_{H-H}$ and larger coupling constants 9.2–11.6 Hz were attributed to $^2J_{P-H}$ couplings (Table 2). The long-range coupling between H-2 and H-4e suggests the presence of a '*W* conformation' of the four σ-bonds between H-2 and H-4e (Fig. 1). From the $^4J_{H-H}$ long-range coupling and the larger $^2J_{P-H}$ coupling constants for H-2 suggest the presence of the $^3T_2$ conformation in the central phospholane ring. Furthermore, the configurations of compounds **8a** and **15b** were determined unambiguously by

Table 2
Chemical shifts (δ values for H-2, H-4′, and H-5′) and long range J_{H-H} and J_{P-H} coupling constants [a] in ^1H , and ^{31}P NMR δ values [b] of compounds **6a–15a** and **11b–15b**





Compound	^1H NMR				^{31}P NMR
	H-2	J_{H-H}, J_{P-H}	H-4′	H-5	
6a	δ 5.59	1.9, 10.3			+68.3
7a	δ 5.53	1.5, 10.0			+68.7
8a	δ 5.00	1.9, 11.0			+70.9
9a	δ 5.41	1.9, 11.1			+70.3
10a	δ 5.00	1.9, 11.1		7.34	+68.8
11a	δ 4.91	1.9, 10.5		7.73	+70.3
11b	δ 5.04	1.9, 10.8	7.28		+71.3
12a	δ 4.77	1.9, 10.0		7.37	+70.0
12b	δ 5.67	2.2, 11.3	7.10		+71.2
13a	δ 6.12	2.1, 11.6		7.82	+69.2
13b	δ 5.31	2.2, 10.3	7.98		+69.0
14a	δ 4.92	1.6, 9.2		7.36	+68.9
14b	δ 4.84	1.6, 9.7	7.44		+69.8
15a	δ 5.09	2.2, 9.2		6.97	+69.6
15b	δ 5.36	1.6, 10.0	7.10		+69.9

[a] Coupling constants (J) values are shown in Hz.
[b] ^{31}P NMR δ values are in ppm.

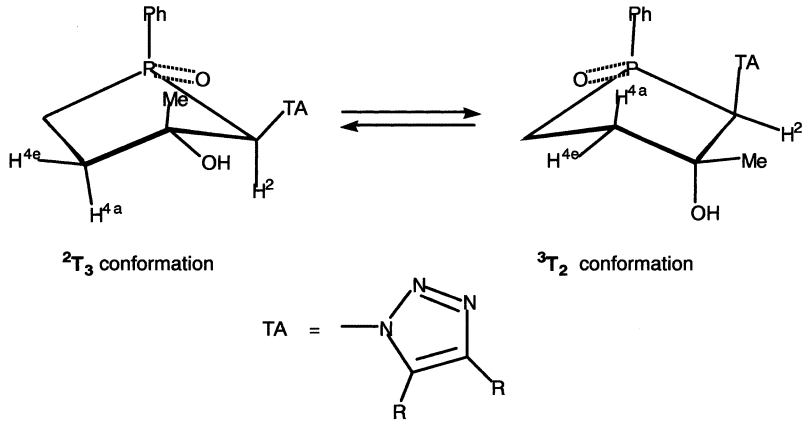


Fig. 1. Favored conformations for the central phospholane ring of nucleosides **6**–**15**, based on ^1H NMR analysis.

single-crystal X-ray crystallography (Figs. 2 and 3). The chemical shifts of H-5′ and H-4′ of the triazole ring in compounds **11a**–**15a** and **11b**–**15b** varied (Table 2) because of the variety of substituents on the triazole ring, but earlier reports showed the characteristic downfield chemical shifts of H-4′ and upfield shift of H-5′ protons.[24] In our studies, regioisomers **11a** and **12a**, having the hydroxy group substituted, exhibited characteristic downfield chemical shifts for H-5′ of the triazole, where as **11b** and **12b** exhibited upfield

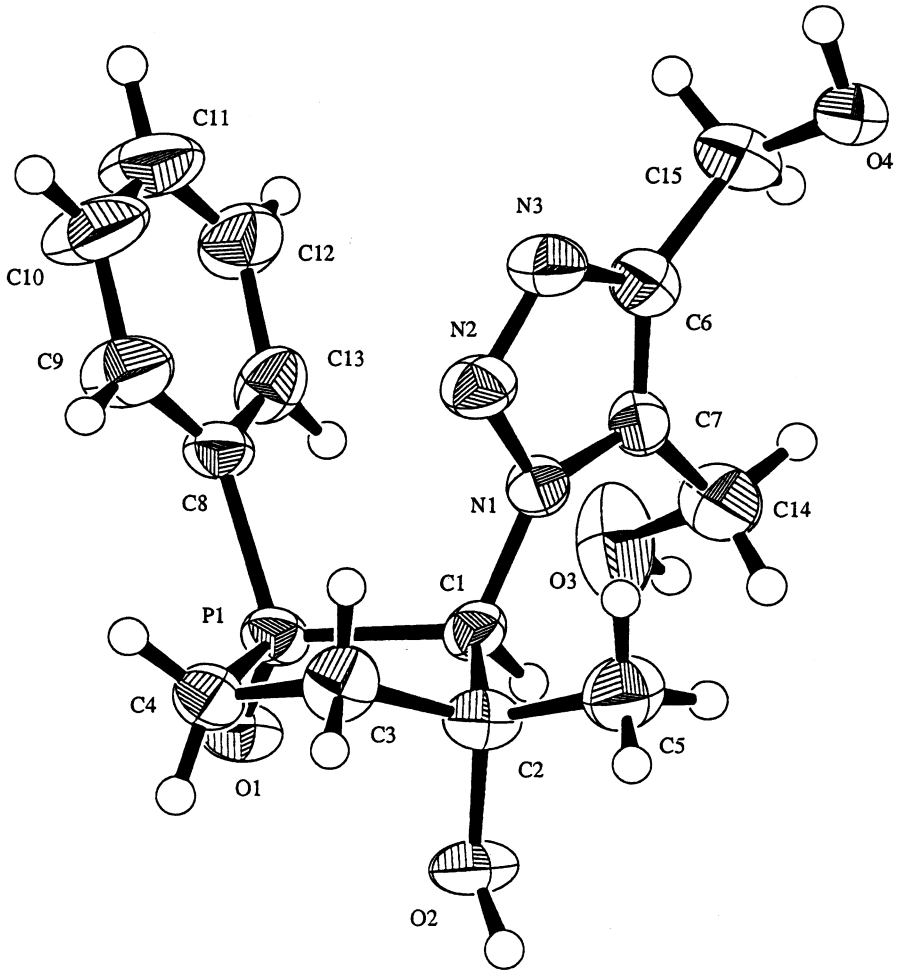


Fig. 2. ORTEP drawing of compound **8a**.

shifts for the triazole H-4′. On the other hand, regioisomers **13a**–**15a** exhibited characteristic upfield shifts for the triazole H-5′ and isomers **13b**–**15b** exhibited downfield shifts for the triazole H-4′ (Table 2). This may be due to the relative magnitude of electron-withdrawing and electron-donating capacities of substituents on the triazole ring. Electron density (MOPAC, PM3) calculations[28] also supported the change in the chemical shifts of the triazole protons in the regioisomers.

Recrystallization of products **6a**–**15a** and **11b**–**15b** from $CHCl_3$ and *n*-hexane produced crystals, but only **8a** and **15b** gave crystals suitable for X-ray studies. Attempts to grow a suitable crystal of regioisomer **15a** was unsuccessful. A single-crystal X-ray study of compounds **8a** and **15b** afforded the structures depicted in Figs. 2 and 3, respectively (see Section 4). The determination of stereochemistry at P-1, C-1, and C-2 [the number according to heterocycle (phospholene) terminology are 1, 2, and 3, respectively] paved the way for establishing the absolute configuration for the phospholane ring as ($1R_P$,2*R*,3*R*) and ($1S_P$,2*S*,3*S*) for its enantiomer.

The X-ray crystallographic studies of compounds **8a** and **15b** revealed that the phenyl ring on phosphorus and the triazole ring at C-1 lie almost parallel (see torsion angles, Table 5). Interestingly, in the crystal packing of compound **8a**, pairs of symmetrically related molecules are linked by P=O···H–O intermolecular hydrogen bonding (Fig. 4) to form dimers. The oxygen atom of the phosphoryl group and hydrogen of the hydroxymethyl group at C-7 of the triazole ring are involved in intermolecular H-bonding linking the symmetrical molecules into dimers (see Fig. 4). The substitution of O by P in the hemiacetal ring caused several changes in the geometry and conformation of the five-mem-

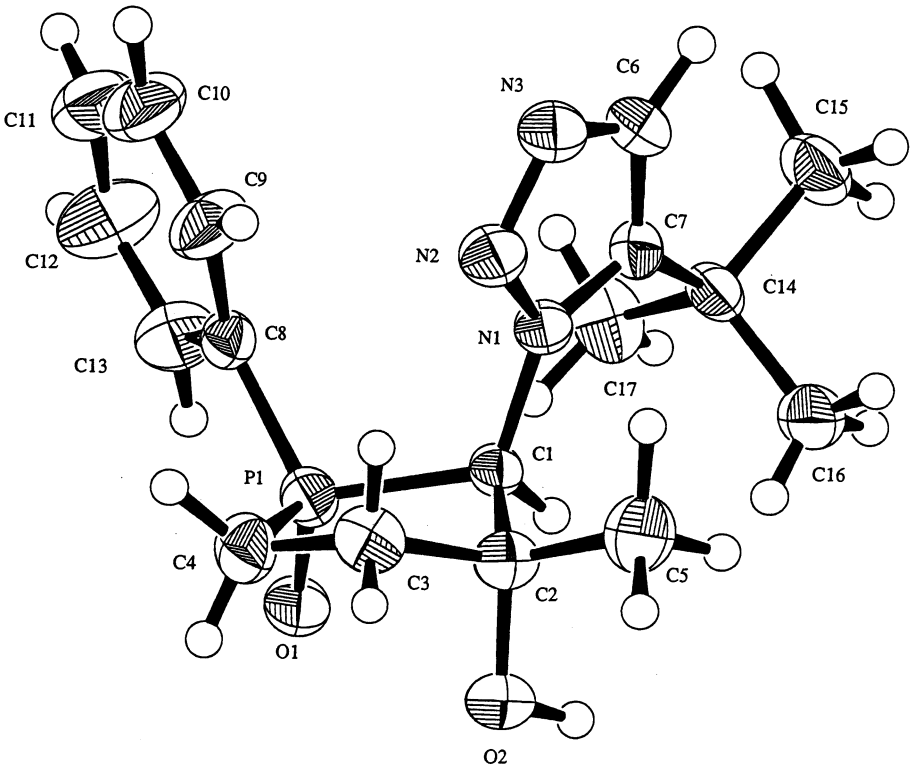


Fig. 3. ORTEP drawing of compound **15b**.

bered ring (Tables 3–6 and Figs. 2 and 3). Considerable changes in the C-1–P-1–C-4 bond angle of the phospha sugars was observed as (96.6°), as compared to the 110° of C-1–O–C-4 in ribofuranose and 93.5° of C-1–S–C-4 in thio sugars.[29] Comparison of the P-1–C-1 and P-1–C-4 bond lengths indicated that the P-1–C-1 bond is longer than that of P-1–C-4 by ~ 0.05 Å. The positive C-1–P-1–C-4–C-3 torsion angle and the negative P-1–C-4–C-3–C-2 torsion angle in the phospholane ring (Table 5) show that the conformation is C-3-exo and C-2-endo. The C-3 atom of the cyclophospholane is displaced by $+0.588$ Å (21.05°) from the best possible four-atom mean-square plane of C-4–P-1–C-1–C-2, and C-2 is displaced by -0.596 Å (21.17°) from the next best possible four-atom mean-square plane C-1–P-1–C-4–C-3, supporting the existence of the $^3T_2$ (C-3-exo and C-2-endo) conformation.[§] Therefore, the conformation of the central phospholane ring is a twisted *envelope* in the solid state.

Preliminary studies on some of the compounds revealed considerable activity and will be reported elsewhere.

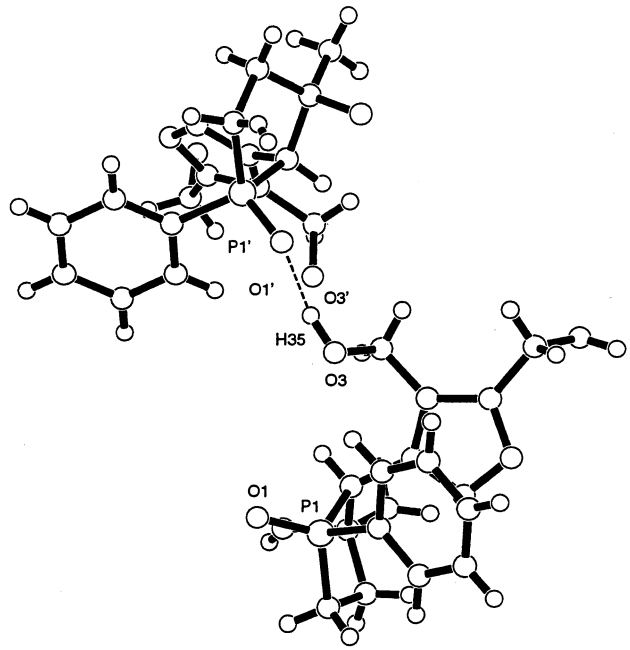


Fig. 4. Intermolecular H-bonding P-1′=O-1′···H-35–O-3 between symmetrically related molecules of **8a**, forming dimers in the crystal packing.

[§] These values are for compound **8a**. For compound **15b**, C-3 is displaced by $+0.468$ (16.81°) Å from the C-4–P-1–C-1–C-2 plane, and C-2 is displaced by -0.607 Å (21.97°) from the C-1–P-1–C-4–C-3 plane.

Table 3
Selected bond lengths (Å) of compounds **8a and 15b**

	Bond lengths [a] (Å)	
	8a	**15b**
P-1–O-1	1.456(7)	1.494(3)
P-1–C-1	1.867(7)	1.861(4)
P-1–C-4	1.824(7)	1.812(5)
P-1–C-8	1.821(7)	1.800(5)
N-1–N-2	1.370(9)	1.359(5)
N-1–C-1	1.449(8)	1.463(5)
N-1–C-7	1.357(8)	1.365(6)
N-2–N-3	1.298(8)	1.316(5)
N-3–N-6	1.367(8)	1.348(6)
C-1–C-2	1.552(9)	1.549(6)
C-2–C-3	1.528(10)	1.525(7)
C-3–C-4	1.520(1)	1.516(7)
C-2–C-5	1.512(10)	1.518(7)
C-6–C-7	1.359(9)	1.374(6)
C-7–C-14	1.478(10)	1.499(6)
C-6–C-15	1.502(9)	

[a] Estimated standard deviations in the least significant figure are given in parentheses.

Table 4
Selected bond angles (°) of compounds **8a** and **15b**

	Bond angles [a] (°)	
	8a	**15b**
O-l–P-1–C-1	114.8(4)	111.7(2)
O-1–P-1–C-4	115.9(3)	115.2(2)
O-1–P-1–C-8	112.7(3)	109.9(2)
C-1–P-1–C-4	95.6(3)	95.6(2)
C-1–P-1–C-8	106.5(3)	112.1(2)
C-4–P-1–C-8	109.8(3)	111.7(2)
N-1–N-2–N-3	106.6(6)	107.2(4)
P-1–C-1–N-1	114.6(5)	116.7(3)
P-1–C-1–C-2	104.0(4)	102.6(3)
N-1–C-1–C-2	114.8(6)	114.4(3)
O-2–C-2–C-1	101.2(5)	105.7(4)
O-2–C-2–C-3	109.5(6)	104.9(4)
C-1–C-2–C-3	106.3(5)	107.2(4)
C-1–C-2–C-5	113.1(6)	113.9(4)
C-3–C-2–C-5	114.0(6)	113.7(4)
C-2–C-3–C-4	109.0(6)	109.1(4)
P-1–C-4–C-3	105.6(5)	107.1(4)
N-3–C-6–C-7	109.1(6)	111.4(4)

[a] Estimated standard deviations in the least significant figure are given in parentheses.

3. Experimental

General methods.—Melting points were recorded on a Yanagimoto MP-S2 micro-melting point apparatus and are uncorrected. Thin-layer chromatography was performed by using 0.2 mm coated silica gel plates. Column chromatography was performed on silica gel Waco gel C-200 using 10:1 mixture of $CHCl_3$ and MeOH as the eluent. ^1H and ^{13}C NMR spectra were recorded on a Jeol GX-270 MHz instrument using Me_4Si as the internal standard and ^{31}P NMR was recorded on a Jeol JNM-EX90 (at 36.18 MHz) instrument using H_3PO_4 as the external standard. Coupling constant (J) values are given in Hz. Mass spectra were recorded on Hitachi RMU7M GC-MS or Shimadzu GCMS-AP5050 gas chromatograph-mass spectrometer instruments using electron impact at 70 eV, and X-ray crystallographic studies were made on a Rigaku AFC7R diffractometer with graphite monochromated Cu K_α radiation and a rotating anode generator. Phase determination was made by a direct method (SIR92).[30]

Table 5
Selected torsion angles of compounds **8a and 15b**

	Torsion Angle [a] (°)	
	8a	**15b**
P-1–C-1–N-1–N-2	58.9(7)	71.2(4)
P-1–C-l–N-1–C-7	−110.3(7)	−110.8(5)
P-1–C-1–C-2–O-2	77.1(5)	70.7(4)
P-1–C-1–C-2–C-3	−37.3(6)	−40.9(4)
P-1–C-1–C-2–C-5	−163.1(6)	−167.6(4)
P-1–C-4–C-3–C-2	−34.7(7)	−26.7(6)
O-1–P-1–C-1–N-1	127.5(5)	136.5(3)
O-1–P-1–C-1–C-2	−106.3(5)	−97.5(3)
O-1–P-1–C-4–C-3	131.4(5)	118.9(4)
O-2–C-2–C-1–N-1	−156.95(5)	−161.9(3)
O-2–C-2–C-3–C-4	−60.4(7)	−66.8(5)
N-1–C-1–P-1–C-4	−110.6(5)	−103.4(4)
N-1–C-1–P-1–C-8	2.0(6)	12.7(4)
N-1–C-1–C-2–C-3	88.8(7)	86.5(5)
N-1–C-1–C-2–C-5	−37.1(8)	−40.2(6)
N-2–N-l–C-1–C-2	−61.4(9)	−48.6(5)
N-3–N-2–N-1–C-1	−174.5(6)	178.3(4)
C-1–P-1–C-4–C-3	10.3(6)	1.7(4)
C-1–P-1–C-8–C-9	−107.6(8)	−61.9(5)
C-1–C-2–C-3–C-4	48.1(7)	45.2(6)
C-2–C-1–P-1–C-4	15.6(5)	22.5(5)
C-2–C-1–P-1–C-8	128.2(5)	138.6(3)
C-3–C-4–P-1–C-8	−99.5(5)	−114.8(4)
C-4–C-3–C-2–C-5	173.4(6)	172.1(5)

[a] The sign is positive if, when looking from atom 2 to atom 3, a clockwise motion of atom 1 would superpose it on atom 4.

Table 6
Summary of crystal data, data collection, and structure solution of compounds **8** and **15b**

Compound	**8**	**15**
Empirical formula	$C_{15}H_{20}N_3PO_4$	$C_{17}H_{24}N_3PO_2$
Formula weight	337.31	333.37
Temperature (K)	296	223
Crystal dimensions (mm)	$0.20 \times 0.20 \times 0.30$	$0.30 \times 0.20 \times 0.20$
Crystal system	orthorhombic	triclinic
Lattice parameters		
a (Å)	14.833(2)	9.611(1)
b (Å)	8.720(2)	11.556(1)
c (Å)	25.951(2)	
α (°)		93.01(1)
β (°)		108.14(1)
γ (°)		111.193(10)
V (Å^3)	3356(1)	873.6(2)
Space group	$Pca2_1$ (no. 29)	$P\bar{1}$ (no. 2)
Z value	8	2
D_{calc} (g/cm^3)	1.335	1.267
F_{000}	1424.00	356.00
μ(Cu K$_\alpha$) (cm^{-1})	16.65	15.01
Total reflections measured	2880	2748
Unique reflections measured ($R_{int} = 0.029$)		2597
Structure solution	direct methods (SIR92)	direct methods (SIR92)
Function minimized	$\Sigma\,\omega(\|F_o\|-\|F_c\|)^2$	$\Sigma\,\omega(\|F_o\|-\|F_c\|)^2$
p-factor	0.0040	0.0320
Observations [$I > 3.00\sigma(I)$]	2289	1636
Residuals: R, R_w	0.038, 0.035	0.056, 0.065

Phospholene 1-oxide was prepared by the reported procedure[31] via the cycloaddition of 2-methyl-1,3-butadiene and phenylphosphonus dichloride.

3-Methyl-1-phenyl-2-phospholene 1-oxide[31].—Isoprene (70 mL, 500 mmol) and phenylphosphonus dichloride (68 mL, 500 mmol) were mixed at rt in a thick-walled flask, sealed and left for 3 weeks. The resultant brown solid was dissolved in $CHCl_3$, poured into ice water and neutralized with $NaHCO_3$. The $CHCl_3$ layer was separated, washed with water (3×200 mL) and dried over anhyd Na_2SO_4. Chloroform was evaporated under diminished pressure and the residue was distilled at 149–150 °C/0.3 mmHg to afford phospholene **1**, 76 g (79%), mp 62 °C; bp[31] 149 °C/0.3 mmHg, mp[31] 60–65 °C.

2-Bromo-3-hydroxy-3-methyl-1-phenylphospholane 1-oxide (**3**).—2-Phospholene **1** (3.41 g, 17.7 mmol) was dissolved in 25 mL of a 4:1 water–$CHCl_3$ mixture and 3.5 mL of Br_2 was added at rt and the solution was stirred for 3 days. To the stirred solution, 40 mL of satd aq Na_2SO_3 was added and the solution stirred for few minutes. After disappearance of the bromine color, the $CHCl_3$ layer was separated and the water layer extracted with $CHCl_3$ (3×30 mL). The combined $CHCl_3$ extracts were washed with water, dried (Na_2SO_4) and evaporated under diminished pressure. The residue was recrystallized from 1:1 $CHCl_3$–hexane.

Compound **3a** (threo), yield: 2.33 g (46%); mp 146–148 °C; IR: ν(cm^{-1}) (neat) 3150 (OH); ^{1}H NMR ($CDCl_3$): δ 7.48–7.91 (m, 5 H, Ph), 5.62 (br s, 1 H, OH), 4.22 (d, 1 H, $J_{2,P}$ 4.0 Hz, H-2), 2.08–2.61 (m, 4 H, H-4,5), 1.66 (s, 3 H, 3-CH_3); ^{13}C NMR ($CDCl_3$): δ 132.5 (d, J 2 Hz, C-3,5 of P-Ph), 131.9 (d, J 10 Hz, C-2,6 of P-Ph), 129.6 (C-4 of P-Ph), 128.1 (d, J 12 Hz, C-1 of P-Ph), 79.5 (d, J 13 Hz, C-3), 50.1 (d, J 66 Hz, C-2), 35.7 (d, J 2 Hz, C-4), 26.0 (d, J 7 Hz, CH_3), 25.4 (d, J 65 Hz, C-5); ^{31}P NMR (H_3PO_4): δ +68.3. Anal. Calcd for $C_{11}H_{14}BrO_2P$: C, 45.70; H, 4.88. Found: C, 45.42; H, 5.02.

2-Azido-3-hydroxy-3-methyl-1-phenylphospholane 1-oxide (**4**).—To a solution of 2-bromophospholane **3a** (3.09 g, 10.7 mmol) in DMF (30 mL) was added NaN_3 (1.27 g, 17.5 mmol) and the mixture stirred at 70 °C for 24 h. DMF was distilled off under diminished pressure and the residue was dissolved in $CHCl_3$ (50 mL) and washed with water ($3 \times$ 20 mL). The $CHCl_3$ layer was dried (Na_2SO_4) and evaporated under diminished pressure. The resultant crude yellow compound was recrystallized from $CHCl_3$ and n-hexane to afford white colorless crystals of **4**, yield: 2.33 g (87%); mp 174–175 °C; IR: ν(cm^{-1}) (neat) 3150 (OH), 2120 (N_3); ^{1}H NMR ($CDCl_3$): δ 7.44–7.78 (m, 5 H, Ph), 5.61 (br s, 1 H, OH), 4.00 (d, 1 H, $J_{2,P}$ 2.1 Hz, H-2), 1.80–2.53 (m, 4 H, H-4,5), 1.46 (s, 3 H, 3-CH_3); ^{13}C NMR ($CDCl_3$): δ 132.6 (d, J 3 Hz, C-3,5 of P-Ph), 131.5 (d, J 10 Hz, C-2,6 of P-Ph), 129.8 (C-4 of P-Ph), 128.6 (d, J 12 Hz, C-1 of P-Ph), 78.7 (d, J 13 Hz, C-3), 67.9 (d, J 73 Hz, C-2), 36.3

(d, *J* 5 Hz, C-4), 26.4 (d, *J* 64 Hz, C-5), and 24.2 (d, *J* 7 Hz, CH_3); ^{31}P NMR (H_3PO_4): δ +66.1. Anal. Calcd for $C_{11}H_{14}N_3O_2P$: C, 52.59; H, 5.62; N, 16.73. Found: C, 52.68; H, 5.38; N, 16.64.

*General procedure for the synthesis of (1*S,*2*R,*3*R*)-3-hydroxy-2-(4- and 5-substituted-1*H*-1,2,3-triazol-1-yl)-3-methyl-1-phenylphospholane 1-oxides* (**6**–**15**).—2-Azidophospholane **4** (0.50 g, 2.0 mmol) and the substituted acetylene **5** (2.0 mmol) were dissolved in 10 mL of dimethoxyethane (DME) and the solution refluxed with stirring. After completion of the reaction (indicated by TLC), solvent was removed under diminished pressure and the product recrystallized from $CHCl_3$ and *n*-hexane. Regioisomers were separated by column chromatography on silica gel using 10:1 $CHCl_3$–MeOH mixture as eluent.

*(1*S,*2*R,*3*R*)-3-Hydroxy-2-(4,5-dimethoxycarbonyl-1*H*-1,2,3-triazol-1-yl)-3-methyl-1-phenylphospholane 1-oxides* (**6a**).—2-Azidophospholane **4** (0.50 g, 2.0 mmol) and dimethylacetylene dicarboxylate (**5a,** 0.43 g, 3.0 mmol) were dissolved in 10 mL of DME and the solution refluxed for 12 h with stirring. The solvent was removed under diminished pressure and the residue was recrystallized from $CHCl_3$ and *n*-hexane to give **6a**, yield: 0.62 g (79%); mp 205–206 °C. ^1H NMR ($CDCl_3$): δ 7.28–7.70 (m, 5 H, Ph), 6.00 (br s, 1 H, OH), 5.59 (dd, 1 H, $J_{2,4}$ 1.9, $J_{2,P}$ 10.3 Hz, H-2), 3.98 (s, 3 H, 5′-$COOCH_3$); 3.87 (s, 3 H, 4′-$COOCH_3$), 2.47–3.00 (m, 4 H, H-4,5), 1.32 (s, 3 H, 3-CH_3); ^{13}C NMR ($CDCl_3$): δ 159.9 (4′-$COOCH_3$), 158.4 (5′-*C*$OOCH_3$), 138.5 (C-4′), 132.9 (C-4 of P-Ph), 131.8 (C-5′), 131.3 (d, *J* 11 Hz, C-2,6 of P-Ph), 128.3 (d, *J* 11 Hz, C-3,5 of P-Ph), 127.0 (d, *J* 12 Hz, C-1 of P-Ph), 80.3 (d, *J* 17 Hz, C-3), 68.3 (d, *J* 66 Hz, C-2), 58.8 (4′-$COOCH_3$), 52.6 (5′-$COOCH_3$), 37.9 (C-4), 25.1 (d, *J* 66 Hz, C-5), 23.6 (d, *J* 7 Hz, CH_3); ^{31}P NMR (H_3PO_4): δ +68.3; EIMS: *m*/*z* 394 $[M+H]^+$, 275 (5), 195 (64), 157 (12), 141 (23), 125 (22), 109 (9), 91 (15), 77 (36), 59 (44), 43 (100). Anal. Calcd for $C_{17}H_{20}N_3O_6P$: C, 51.91; H, 5.12; N, 10.68. Found: C, 51.68; H, 5.06; N, 10.57.

*(1*S,*2*R,*3*R*)-3-Hydroxy-2-(4,5-diethoxycarbonyl-1*H*-1,2,3-triazol-1-yl)-3-methyl-1-phenylphospholane 1-oxide* (**7a**).—2-Azidophospholane **4** (0.50 g, 2.0 mmol) and diethylacetylene dicarboxylate (**5b**, 0.51 g, 3.0 mmol) in 10 mL of DME were refluxed for 16 h with stirring. The solvent was evaporated under diminished pressure and the residue recrystallized from $CHCl_3$ and *n*-hexane to give **7a**, yield: 0.71 g (84%); mp 175–176 °C; ^1H NMR ($CDCl_3$): δ 7.29–7.68 (m, 5 H, Ph), 5.53 (dd, 1 H, $J_{2,4}$ 1.6, $J_{2,P}$ 10.0 Hz, H-2), 4.42 (q, 2 H, $J_{H,H}$ 7.2 Hz, 4′-$COOCH_2CH_3$), 4.31(q, 2 H, $J_{H,H}$ 7.2 Hz, 5′-$COOCH_2CH_3$), 3.75 (br s, 1 H, OH), 2.47–3.00 (m, 4 H, H-4,5), 1.37 (t, 3 H, $J_{H,H}$ 7.2 Hz, 4′-$COOCH_2CH_3$); 1.33 (t, 3 H, $J_{H,H}$ 7.2 Hz, 5′-$COOCH_2CH_3$), 1.32 (s, 3 H, 3-CH_3); ^{13}C NMR ($CDCl_3$): δ 159.5 (4′-*C*OOEt), 158.1 (5′-*C*OOEt), 138.8 (C-4′), 132.9 (C-4 of P-Ph), 131.7 (C-5′), 131.3 (d *J* 10 Hz, C-2,6 of P-Ph), 128.3 (d, *J* 12 Hz, C-3,5 of P-Ph), 127.4 (d, *J* 92 Hz, C-1 of P-Ph), 80.4 (d, *J* 17 Hz, C-3), 68.2 (d, *J* 67 Hz, C-2), 63.3 (4′-$COOCH_2CH_3$), 61.8 (5′-$COOCH_2CH_3$), 37.9 (C-4), 25.0 (d, *J* 66 Hz, C-5), 23.6 (d, *J* 6 Hz, CH_3), 14.1 (4′-$COOCH_2CH_3$), 13.8 (5′-$COOCH_2CH_3$); ^{31}P NMR (H_3PO_4): δ +68.7; EIMS: *m*/*z* 422 $[M+H]^+$, 275 (16), 207 (3), 195 (94), 179 (6), 157 (8), 141 (28), 125 (31), 109 (9), 91 (17), 77 (33) and 43 (100). Anal. Calcd for $C_{19}H_{24}N_3O_6P$: C, 54.16; H, 5.74; N, 9.97. Found: C, 54.00; H, 5.70; N, 9.83.

*(1*S,*2*R,*3*R*)-3-Hydroxy-2-(4,5-dihydroxymethyl-1*H*-1,2,3-triazol-1-yl)-3-methyl-1-phenylphospholane 1-oxide* (**8a**).—2-Azidophospholane **4** (0.50 g, 2.0 mmol) and 2-butyn-1,4-diol (**5c**, 0.30 g, 3.4 mmol) in 10 mL of DME were refluxed for 75 h with stirring. The solvent was evaporated under diminished pressure and recrystallized from $CHCl_3$ and *n*-hexane to give **8a**, yield: 0.46 g (68%); mp 205–206 °C; ^1H NMR ($CDCl_3$): δ 7.26–7.61 (m, 5 H, Ph), 5.65 (br s, 1 H, OH), 5.00 (dd, 1 H, $J_{2,4}$ 1.9, $J_{2,P}$ 11.0 Hz, H-2), 4.60 (s, 2 H, 4′-CH_2OH), 4.43 (s, 2 H, 5′-CH_2OH), 3.52 (br s, 2 H, 4′,5′-CH_2OH), 2.42–2.97 (m, 4 H, H-4,5), 1.25 (s, 3 H, 3-CH_3); ^{13}C NMR ($CDCl_3$): δ 143.7 (C-4′), 135.1 (C-5′), 132.5 (d, *J* 2 Hz, C-4 of P-Ph), 130.9 (d, *J* 10 Hz, C-2,6 of P-Ph), 127.9 (d, *J* 12 Hz, C-3,5 of P-Ph), 127.5 (d, *J* 94 Hz, C-1 of P-Ph), 79.6 (d, *J* 17

Hz, C-3), 67.1 (d, *J* 70 Hz, C-2), 54.4 (4′-*C*H_2OH), 50.6 (5′-*C*H_2OH), 37.8 (C-4), 24.7 (d, *J* 66 Hz, C-5), 23.1 (d, *J* 7 Hz, CH_3); ^{31}P NMR (H_3PO_4): δ +70.9. Anal. Calcd for $C_{15}H_{20}N_3O_4P$: C, 53.41; H, 5.98; N, 12.46. Found: C, 53.10; H, 5.97; N, 12.19.

*(1*S,*2*R,*3*R*)-3-Hydroxy-2-(4,5-dicarboxyl-1*H*-1,2,3-triazol-1-yl)-3-methyl-1-phenylphospholane 1-oxide* (**9a**).—2-Azidophospholane **4** (0.38 g, 1.5 mmol) and acetylenedicarboxylic acid (**5d**, 0.18 g, 1.6 mmol) in 10 mL of DME were refluxed for 24 h with stirring. The solvent was evaporated under diminished pressure and the residue recrystallized from $CHCl_3$–MeOH and *n*-hexane to give **9a**, yield: 0.43 g (79%); mp 175–176 °C. ^{1}H NMR (CD_3OD): δ 7.32–7.63 (m, 5 H, Ph), 5.41 (dd, 1 H, $J_{2,4}$ 1.9, $J_{2,P}$11.1 Hz, H-2), 2.20–3.05 (m, 4 H, H-4,5), 1.28 (s, 3 H, 3-CH_3); ^{13}C NMR (CD_3OD): δ 163.3 (4′-*C*OOH), 157.7 (5′-*C*OOH), 137.9 (C-4′), 132.3 (C-4 of P-Ph), 131.5 (C-5′), 130.3 (d, *J* 10 Hz, C-2,6 of P-Ph), 127.8 (d, *J* 11 Hz, C-3,5 of P-Ph), 127.7 (C-1 of P-Ph was not clear), 79.3 (d, *J* 16 Hz, C-3), 68.6 (d, *J* 68 Hz, C-2), 37.6 (C-4), 24.5 (d, *J* 66 Hz, C-5), 22.8 (d, *J* 7 Hz, CH_3); ^{31}P NMR (H_3PO_4): δ +70.3. Anal. Calcd for $C_{15}H_{16}N_3O_6P$: C, 49.32; H, 4.41; N, 11.50. Found: C, 48.98; H, 4.51; N, 11.05.

*(1*S,*2*R,*3*R*)-3-Hydroxy-2-(4-trimethylsilyl-1*H*-1,2,3-triazol-1-yl)-3-methyl-1-phenylphospholane 1-oxide* (**10a**).—2-Azidophospholane **4** (0.20 g, 0.80 mmol) and (trimethylsilyl)acetylene (**5e**, 0.20 g, 2.0 mmol) in 10 mL of DME were refluxed for 24 h with stirring. The solvent was evaporated under diminished pressure and the residue recrystallized from $CHCl_3$ and *n*-hexane to give **10a**, yield: 0.16 g (57%); mp 221–222 °C. ^{1}H NMR ($CDCl_3$): δ 7.20–7.70 (m, 5 H, Ph), 7.34 (s, 1 H, H-5′), 6.36 (br s, 1 H, OH), 5.00 (dd, 1 H, $J_{2,4}$ 1.9, $J_{2,P}$ 11.1 Hz, H-2), 2.35–3.25 (m, 4 H, H-4,5), 1.46 (s, 3 H, 3-CH_3), 0.12 (s, 9 H, 5′-Si(CH_3)$_3$); ^{13}C NMR ($CDCl_3$): δ 145.9 (C-4′), 132.4 (d, *J* 3 Hz, C-4 of P-Ph), 130.9 (d, *J* 10 Hz, C-2,6 of P-Ph), 130.8 (C-5′), 128.0 (d, *J* 11 Hz, C-3,5 of P-Ph), 127.9 (d, *J* 93 Hz, C-1 of P-Ph), 79.8 (d, *J* 16 Hz, C-3), 68.5 (d, *J* 69 Hz, C-2), 38.0 (d, *J* 4 Hz, C-4), 25.2 (d, *J* 63 Hz, C-5), 24.0 (d, *J* 7 Hz, CH_3), 0.00 (s, 3 C, Si(CH_3)$_3$; ^{31}P NMR (H_3PO_4): δ +68.8. Anal. Calcd for $C_{16}H_{24}N_3O_2PSi$: C, 54.99; H, 6.92; N, 12.02. Found: C, 54.59; H, 7.02; N, 11.89.

*(1*S,*2*R,*3*R*)-3-Hydroxy-2-(4-hydroxymethyl-1*H*-1,2,3-triazol-1-yl)-3-methyl-1-phenylphospholane 1-oxide* (**11a**) *and (1*S,*2*R,*3*R*)-3-hydroxy-2-(5-hydroxymethyl-1*H*-1,2,3-triazol-1-yl)-3-methyl-1-phenylphospholane 1-oxide* (**11b**).—2-Azidophospholane **4** (0.75 g, 3.0 mmol) and propargyl alcohol (**5f**, 0.56 g, 10 mmol) were dissolved in 10 mL of DME and refluxed for 48 h with stirring. The solvent was removed and the residue separated by column chromatography on silica gel using 10:1 $CHCl_3$–MeOH as eluent, giving two compounds. Compound **11a**, yield: 0.33 g (36%); mp 184–185 °C. ^{1}H NMR (CD_3OD): δ 7.73 (s, 1 H, H-5′), 7.32–7.66 (m, 5 H, Ph), 4.91 (dd, 1 H, $J_{2,4}$ 1.9, $J_{2,P}$ 10.5 Hz, H-2), 4.37 (s, 2 H, 4′-CH_2OH), 2.39–2.99 (m, 4 H, H-4,5), 1.19 (s, 3 H, 3-CH_3), OH peaks were not observed by H/D exchange; ^{13}C NMR (CD_3OD): δ 147.3 (C-4′), 132.7 (C-5′), 131.0 (d, *J* 10 Hz, C-2,6 of P-Ph), 128.1 (d, *J* 12 Hz, C-3,5 of P-Ph), 127.1 (C-1 of Ph not clear), 124.0 (d, *J* 9 Hz, C-4 of P-Ph) 79.2 (d, *J* 18 Hz, C-3), 69.9 (d, *J* 70 Hz, C-2), 55.3 (4-*C*H_2OH), 37.8 (C-4), 24.6 (d, *J* 74 Hz, C-5), 23.3 (CH_3); ^{31}P NMR (H_3PO_4): δ +70.3; EIMS: *m*/*z* 308 $[M+H]^+$, 261 (2), 242 (8), 207 (3), 215 (6), 196 (23), 195 (18), 179 (2), 164 (16), 157 (12), 141 (16), 125 (19), 117 (12), 109 (9), 91 (35), 77 (49), 55 (64), 47 (100), 43 (73). Anal. Calcd for $C_{14}H_{18}N_3O_3P{\cdot}0.5\ H_2O$: C, 51.69; H, 6.19; N, 12.91. Found: C, 51.59; H, 6.18; N, 12.79.

Compound **11b**, yield: 0.35 g (38%); mp 227–228 °C. ^{1}H NMR ($CDCl_3$): δ 7.30–7.66 (m, 5 H, Ph), 7.28 (s, 1 H, H-4′), 5.04 (dd, 1 H, $J_{2,4}$ 1.9, $J_{2,P}$ 10.8 Hz, H-2), 4.61 (s, 2 H, 5′-CH_2OH), 2.35–3.02 (m, 4 H, H-4,5), 1.20 (s, 3 H, 3-CH_3); ^{13}C NMR ($CDCl_3$): δ 140.6 (C-4′), 134.5 (d, *J* 4 Hz, C-5′), 133.3 (d *J* 15 Hz, C-2,6 of P-Ph), 133.0 (C-4 of P-Ph), 130.4 (d, *J* 94 Hz, C-1 of P-Ph), 130.1 (d, *J* 12 Hz, C-3,5 of P-Ph), 81.6 (d, *J* 17 Hz, C-3), 69.5 (d, *J* 70 Hz, C-2), 55.7 (5′-*C*H_2OH), 40.0 (d, *J* 5 Hz, C-4), 26.1 (d, *J* 66 Hz, C-5), 24.7 (d, *J* 7 Hz, CH_3); ^{31}P NMR (H_3PO_4): δ +71.3; *m*/*z* 308 $[M+H]^+$, 261 (4), 208 (2), 196 (32), 195 (24), 179 (2), 157 (20), 141 (21), 125 (18), 109 (9), 91 (21), 77 (43), 55 (46), 43 (100). Anal.

Calcd for $C_{14}H_{18}N_3O_3P$: C, 54.72; H, 5.90; N, 13.67. Found: C, 54.89; H, 6.00; N, 13.64.

*(1*S*,2*R*,3*R*)-3-Hydroxy-2-[4-(1-hydroxy-1-methylethyl)-1*H*-1,2,3-triazol-1-yl]-3-methyl-1-phenylphospholane 1-oxide* (**12a**) *and (1*S*,2*R*,3*R*)-3-hydroxy-2-[5-(1-hydroxy-1-methylethyl)-1*H*-1,2,3-triazol-1-yl]-3-methyl-1-phenylphospholane 1-oxide* (**12b**).—2-Azidophospholane **4** (0.50 g, 2.0 mmol) and 2-methyl-3-butyn-2-ol (**5g**, 0.25 g, 3.0 mmol) were dissolved in 10 mL of DME and refluxed for 5 days with stirring. The solvent was removed and the residue separated by column chromatography on silica gel using 10:1 $CHCl_3$–MeOH as eluent.

Compound **12a**, yield: 0.28 g (42%); mp 204–205 °C. ^{1}H NMR ($CDCl_3$): δ 7.26–7.57 (m, 5 H, Ph), 7.37 (s, 1 H, H-5′), 4.77 (dd, 1 H, $J_{2,4}$ 1.9, $J_{2,P}$ 10.0 Hz, H-2), 2.40–3.01 (m, 4 H, H-4,5), 1.38 (s, 3 H, 4′-C(CH_3)$_2$), 1.34 (s, 3 H, 4′-C(CH_3)$_2$), 1.26 (s, 3 H, 3-CH_3), OH peaks were not clear; ^{13}C NMR ($CDCl_3$): δ 155.3 (C-4′), 132.5 (C-5′), 130.7 (d, *J* 10 Hz, C-2,6 of P-Ph), 127.9 (d, *J* 12 Hz, C-3,5 of P-Ph), 127.5 (d, *J* 94 Hz, C-1 of P-Ph), 121.5 (C-4 of P-Ph), 79.0 (d, *J* 17 Hz, C-3), 69.7 (d, *J* 70 Hz, C-2), 67.6 (4′-*C*(CH$_3$)$_2$OH), 37.8 (C-4), 29.9 and 29.5 (4′-C(*C*H$_3$)$_2$OH), 24.4 (d, *J* 65 Hz, C-5), 23.2 (d, *J* 6 Hz, CH_3); ^{31}P NMR (H_3PO_4): δ +70.0. Anal. Calcd for $C_{16}H_{22}N_3O_3P$: C, 57.31; H, 6.61; N, 12.53. Found: C, 57.14; H, 6.64; N, 12.37.

Compound **12b**, yield: 0.17 g (25%); mp 215–216 °C. ^{1}H NMR ($CDCl_3$): δ 7.25–7.68 (m, 5 H, Ph), 7.10 (s, 1 H, 4′-H), 5.67 (dd, 1 H, $J_{2,4}$ 2.2, $J_{2,P}$ 11.3 Hz, H-2), 2.37–3.11 (m, 4 H, H-4,5), 1.58 (s, 3 H, 5′-C(CH_3)$_2$OH), 1.48 (s, 3 H, 5′-C(CH_3)$_2$OH), 1.27 (s, 3 H, 3-CH_3), OH peaks not observed; ^{13}C NMR ($CDCl_3$): δ 144.4 (C-4′), 132.3 (d, *J* 4 Hz, C-5′), 131.4 (d, *J* 10 Hz, C-2,6 of P-Ph), 129.3 (C-4 of P-Ph), 127.6 (d, *J* 94 Hz, C-1 of P-Ph), 127.5 (d, *J* 12 Hz, C-3,5 of P-Ph), 79.8 (d, *J* 18 Hz, C-3), 68.1 (d, *J* 71 Hz, C-2), 66.3 (5′-*C*(CH$_3$)$_2$OH), 37.9 (d, *J* 5 Hz, C-4), 30.4 and 30.3 (5′-C(*C*H$_3$)$_2$OH), 24.9 (d, *J* 66 Hz, C-5), 23.1 (d, *J* 7 Hz, CH_3); ^{31}P NMR (H_3PO_4): δ +71.2. Anal. Calcd for $C_{16}H_{22}N_3O_3P{\cdot}0.5\ H_2O$: C, 55.80; H, 6.73; N, 12.20. Found: C, 55.68; H, 6.78; N, 12.13.

*(1*S*,2*R*,3*R*)-3-Hydroxy-2-(4-methoxycarbonyl-1*H*-1,2,3-triazol-1-yl)-3-methyl-1-phenylphospholane 1-oxide* (**13a**) *and (1*S*,2*R*,3*R*)-3-hydroxy-2-(5-methoxycarbonyl-1*H*-1,2,3-triazol-1-yl)-3-methyl-1-phenylphospholane 1-oxide* (**13b**).—2-Azidophospholane **4** (0.50 g, 2.0 mmol) and propargylic acid methyl ester (**5h**, 0.25 g, 3.0 mmol) were dissolved in 10 mL of DME and refluxed for 12 h with stirring. The solvent was removed and the residue separated by column chromatography on silica gel using 10:1 $CHCl_3$–MeOH as eluent.

Compound **13a**, yield: 0.33 g (49%); mp 206–207 °C. ^{1}H NMR ($CDCl_3$): δ 7.82 (s, 1 H, H-5′), 7.23–7.66 (m, 5 H, Ph), 6.12 (dd, 1 H, $J_{2,4}$ 2.1, $J_{2,P}$ 11.6 Hz, H-2), 5.82 (br s, 1 H, OH), 3.83 (s, 3 H, 4′-COOCH_3), 2.48–3.01 (m, 4 H, H-4,5), 1.38 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$): δ 160.8 (4′-*C*OOMe), 139.0 (C-4′), 133.1 (d, *J* 2 Hz, C-5′), 131.2 (d, *J* 10 Hz, C-2,6 of P-Ph), 129.4 (C-4 of P-Ph), 128.4 (d, *J* 12 Hz, C-3,5 of P-Ph), 127.2 (d, *J* 93 Hz, C-1 of P-Ph), 79.9 (d, *J* 17 Hz, C-3), 69.7 (d, *J* 67 Hz, C-2), 52.2 (5′-COO*C*H$_3$), 37.8 (d, *J* 4 Hz, C-4), 25.2 (d, *J* 66 Hz, C-5), 23.7 (d, *J* 6 Hz, CH_3); ^{31}P NMR (H_3PO_4): δ +69.2. Anal. Calcd for $C_{15}H_{18}N_3O_4P{\cdot}0.5\ H_2O$: C, 52.32; H, 5.56; N, 12.20. Found C, 52.28; H, 5.38; N, 11.99.

Compound **13b**, yield: 0.25 g (37%); mp 219–220 °C. ^{1}H NMR ($CDCl_3$): δ 7.98 (s, 1 H, H-4′), 7.21–7.67 (m, 5 H, Ph), 5.94 (br s, 1 H, OH), 5.31 (dd, 1 H, $J_{2,4}$ 2.2, $J_{2,P}$ 10.3 Hz, H-2), 3.86 (s, 3 H, 5′-COOCH_3), 2.51–3.03 (m, 4 H, H-4,5), 1.32 (s, 3 H, 3-CH_3); ^{13}C NMR ($CDCl_3$): δ 160.6 (5′-*C*OOMe), 139.0 (C-4′), 133.1 (d, *J* 2 Hz, C-5′), 131.3 (d, *J* 10 Hz, C-2,6 of P-Ph), 129.4 (d, *J* 2 Hz, C-4 of P-Ph), 128.5 (d, *J* 12 Hz, C-3,5 of P-Ph), 127.2 (d, *J* 93 Hz, C-1 of P-Ph), 80.0 (d, *J* 16 Hz, C-3), 69.7 (d, *J* 68 Hz, C-2), 52.2 (5′-COO*C*H$_3$), 37.3 (d, *J* 4 Hz, C-4), 25.2 (d, *J* 66 Hz, C-5), 23.7 (d, *J* 6 Hz, CH_3); ^{31}P NMR (H_3PO_4): δ +69.0. Anal. Calcd for $C_{15}H_{18}N_3O_4P$: C, 53.73; H, 5.41; N, 12.53. Found: C, 53.43; H, 5.44; N, 12.53.

*(1*S*,2*R*,3*R*)-3-Hydroxy-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-3-methyl-1-phenylphospholane 1-oxide* (**14a**) *and (1*S*,2*R*,3*R*)-3-hydroxy-2-(5-phenyl-1*H*-1,2,3-triazol-1-yl)-3-*

methyl-1-phenylphospholane 1-oxide (**14b**).—2-Azidophospholane **4** (0.50 g, 2.0 mmol) and phenylacetylene (**5i**, 0.31 g, 3.0 mmol) were dissolved in 10 mL of DME and refluxed for 4 days with stirring. The solvent was removed and the residue separated by column chromatography on silica gel using 10:1 $CHCl_3$–MeOH as eluent.

Compound **14a**, yield: 0.23 g (33%); mp 230–232 °C. ^{1}H NMR ($CDCl_3$): δ 7.05–7.67 (m, 10 H, Ph), 7.36 (s, 1 H, H-5′), 5.15 (br s, 1 H, OH), 4.92 (dd, 1 H, $J_{2,4}$ 1.6, $J_{2,P}$ 9.2 Hz, H-2), 2.35–3.19 (m, 4 H, H-4,5), 1.27 (s, 3 H, 3-CH_3); ^{13}C NMR ($CDCl_3$): δ 139.4 (C-4′), 132.8 (d, *J* 4 Hz, C-5′), 132.5 (C-2,6 of 4′-Ph), 131.4 (d, *J* 10 Hz, C-2,6 of P-Ph), 129.7 (C-4 of 4′-Ph), 129.3 (d, *J* 6 Hz, C-4 of P-Ph), 128.2 (d, *J* 12 Hz, C-3,5 of P-Ph), 127.8 (d, *J* 93 Hz, C-1 of P-Ph), 125.8 (C-3,5 of 4′-Ph), 123.3 (C-1 of 4′-Ph), 80.7 (d, *J* 18 Hz, C-3), 66.6 (d, *J* 70 Hz, C-2), 38.2 (d, *J* 4 Hz, C-4), 25.1 (d, *J* 66 Hz, C-5), 23.8 (d, *J* 6, CH_3); ^{31}P NMR (H_3PO_4): δ +68.9. Anal. Calcd for $C_{19}H_{20}N_3O_2P$: C, 64.58; H, 5.70; N, 11.89. Found: C, 64.22; H, 5.71; N, 11.82.

Compound **14b**, yield: 0.12 g (17%); mp 228–229 °C. ^{1}H NMR ($CDCl_3$): δ 7.44 (s, 1 H, H-4′), 7.29–7.65 (m, 10 H, Ph), 4.84 (dd, 1 H, $J_{2,4}$ 1.6, $J_{2,P}$ 9.7 Hz, H-2), 2.43–3.02 (m, 4 H, H-4,5), 1.33 (s, 3 H, 3-CH_3), OH peak was not observed clearly; ^{13}C NMR ($CDCl_3$): δ 146.8 (C-4′), 132.6 (d, *J* 4 Hz, C-5′), 130.7 (d, *J* 10 Hz C-2,6 of P-Ph), 129.2 (C-4 of 5′-Ph), 128.5 (C-4 of P-Ph), 128.1 (C-3,5 of 5′-Ph), 127.9 (d, *J* 12 Hz, C-3,5 of P-Ph), 125.3 (C-2,6 of 5′-Ph), 121.9 (C-1 of 5′-Ph), 78.8 (d, *J* 17 Hz, C-3), 69.8 (d, *J* 70 Hz, C-2), 37.7 (C-4), 24.2 (d, *J* 65 Hz, C-5), 23.0 (d, *J* 6 Hz, CH_3), C-1 of P-Ph not clear; ^{31}P NMR (H_3PO_4): δ +69.8. Anal. Calcd for $C_{19}H_{20}N_3O_2P$: C, 64.58; H, 5.70; N, 11.89. Found: C, 64.21; H, 5.78; N, 11.75.

*(1*S*,2*R*,3*R*)-3-Hydroxy-2-(4-*t*-butyl-1*H*-1,2,3-triazol-1-yl)-3-methyl-1-phenylphospholane 1-oxide* (**15a**) *and (1*S*,2*R*,3*R*)-3-hydroxy-2-(5-*t*-butyl-1*H*-1,2,3-triazol-1-yl)-3-methyl-1-phenylphospholane 1-oxide* (**15b**).—2-Azidophospholane **4** (0.50 g, 2.0 mmol) and 3,3-dimethyl-1-butyne (**5j**, 0.33 g, 4.0 mmol) were dissolved in 10 mL of DME and refluxed for 36 h with stirring. The solvent was removed and the residue separated by column chromatography on silica gel using 10:1 $CHCl_3$–MeOH as eluent.

Compound **15a**, yield: 0.37 g (55%); mp 224–227 °C. ^{1}H NMR ($CDCl_3$): δ 7.26–7.59 (m, 5 H, Ph), 6.97 (s, 1 H, H-5′), 5.88 (br s, 1 H, OH), 5.09 (dd, 1 H, $J_{2,4}$ 2.2, $J_{2,P}$ 9.2 Hz, H-2), 2.47–3.15 (m, 4 H, H-4,5), 1.49 (s, 3 H, 3-CH_3), 1.08 (s, 9 H, 4′-C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$): δ 157.0 (C-4′), 132.5 (C-5′), 131.0 (d, *J* 10 Hz C-2,6 of P-Ph), 128.1 (d, *J* 12 Hz, C-3,5 of P-Ph), 127.8 (d, *J* 93 Hz, C-1 of P-Ph), 120.6 (C-4 of P-Ph), 79.9 (d, *J* 17 Hz, C-3), 69.1 (d, *J* 70 Hz, C-2), 38.1 (d, *J* 1 Hz, C-4), 30.3 (5′-*C*(CH_3)$_3$), 30.1 (5′-C(*C*H_3)$_3$), 25.3 (d, *J* 65 Hz, C-5), 24.0 (d, *J* 7 Hz, CH_3); ^{31}P NMR (H_3PO_4): δ +69.6. Anal. Calcd for $C_{17}H_{24}N_3O_2P$: C, 61.25; H, 7.25; N, 12.60. Found: C, 60.87; H, 7.35; N, 12.47.

Compound **15b**, yield: 0.14 g (21%), mp 247–250 °C. ^{1}H NMR ($CDCl_3$): δ 7.28–7.72 (m, 5 H, Ph), 7.10 (s, 1 H, H-4′), 6.13 (br s, 1 H, OH), 5.36 (dd, 1 H, $J_{2,4}$ 1.6, $J_{2,P}$ 10.0 Hz, H-2), 2.44–3.21 (m, 4 H, H-4,5), 1.35 (s, 9 H, 5′-C(CH_3)$_3$), 1.25 (s, 3 H, 3-CH_3); ^{13}C NMR ($CDCl_3$): δ 146.7 (C-4′), 132.6 (d, *J* 4 Hz, C-5′), 131.9 (d, *J* 10 Hz C-2,6 of P-Ph), 130.2 (C-4 of P-Ph), 127.9 (d, *J* 93 Hz, C-1 of P-Ph), 127.8 (d, *J* 12 Hz, C-3,5 of P-Ph), 81.0 (d, *J* 18 Hz, C-3), 67.8 (d, *J* 68 Hz, C-2), 38.4 (C-4), 30.2 (5′-*C*(CH_3)$_3$), 30.0 (5′-C(*C*H_3)$_3$), 25.6 (d, *J* 66 Hz, C-5), 23.7 (d, *J* 7 Hz, CH_3); ^{31}P NMR (H_3PO_4): δ +69.9. Anal. Calcd for $C_{17}H_{24}N_3O_2P$: C, 61.25; H, 7.25; N, 12.60. Found: C, 61.05; H, 7.37; N, 12.46.

4. Supplementary material

Full crystallographic details excluding structure features have been deposited with the Cambridge Crystallographic Data Centre (CCDC). These data may be obtained, on request, from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Tel. +44-1223-336408; fax. +44-1223-336033; e-mail. deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

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