New hydrophosphoryl compounds derived from *ent*-16-oxobeyeran-19-oic acid

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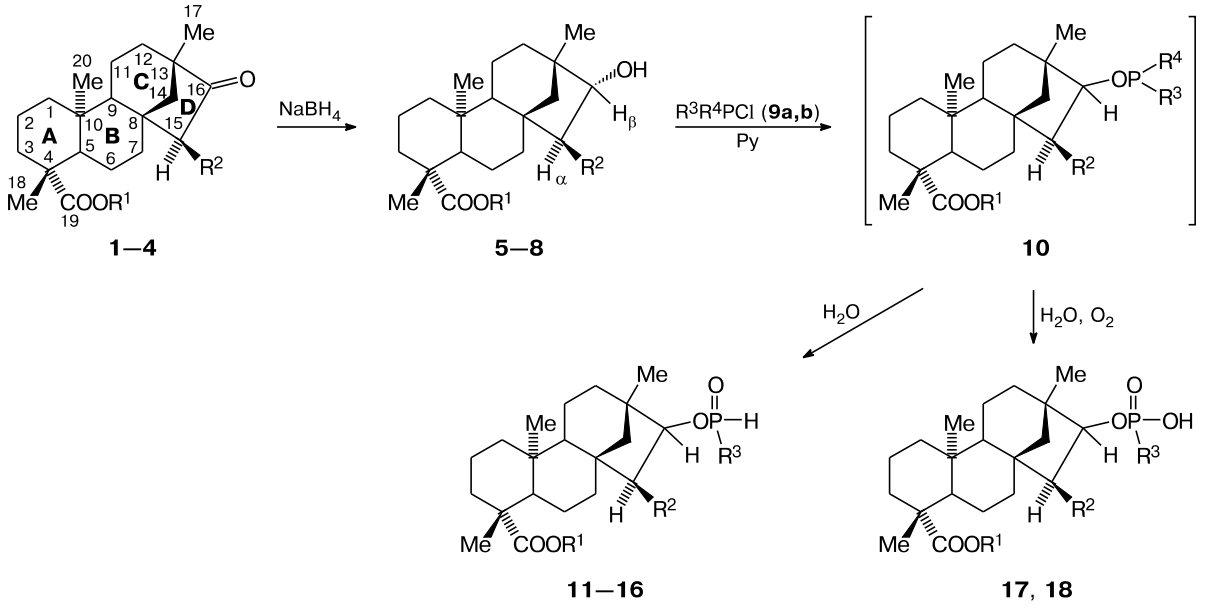
A number of 16-hydroxy derivatives were obtained from *ent*-16-oxobeyeran-19-oic acid, O-phosphorylation of which with subsequent hydrolysis led to the corresponding hydrophosphoryl compounds. Their diastereomeric composition was studied.

Key words: *ent*-16-oxobeyeran-19-oic acid, isosteviol, triterpenoids, phosphorylation, hydrophosphoryl compounds, diethyl chlorophosphite, phenyl dichlorophosphonite, diastereomers.

Hydrophosphoryl compounds are widely used in organophosphorus synthesis,[1] however, there are just scarce examples of their modification with chiral substituents and preparation of enantiopure compounds.[2] *ent*-16-Oxobeyeran-19-oic acid (**1**) (Scheme 1), also called isosteviol, is one of the naturally occuring enantiopure compounds, which is readily available from the stevia plant.[3] Earlier, we have described[4] the first example of hydrophosphoryl derivative of compound **1** obtained by the reaction of PCl_3 with methyl *ent*-16α-hydroxybeyeran-19-oate (the process involved the hydroxy group) with subsequent transformation of the intermediately formed dichlorophosphitobeyeranoate to the corresponding monoalkyl phosphite.

In the present work, we describe obtaining of new hydrophosphoryl derivatives based on compounds **1**—**4**, which initially were converted to hydroxy derivatives **5**—**8**.

Scheme 1



Compound	R^1	R^2	Compound	R^1	R^2	R^3	Compound	R^1	R^2	R^3
1, **5**	H	H	**11**	H	H	OEt	**15**	H	H	Ph
2, **6**	Me	H	**12**	Me	H	OEt	**16**	Me	H	Ph
3, **7**	H	Cl	**13**	H	Cl	OEt	**17**	H	H	Ph
4, **8**	Me	Br	**14**	Me	Br	OEt	**18**	Me	H	Ph

9a: $R^3 = R^4 = OEt$
9b: R^3= Ph, R^4 = Cl

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The reaction of the latter with diethyl chlorophosphite (**9a**) and phenyl dichlorophosphonite (**9b**) in the presence of pyridine proceeded at the hydroxy group and gave rise to the desired O-phosphorylation products.

Results and Discussion

In order to prepare compounds suitable for phosphorylation, we carried out the reduction of compound **1**, its methyl ester (**2**), as well as 15-chloro and 15-bromo derivatives (**3** and **4**, respectively), using procedures described earlier.[5—8] The hydroxy derivatives thus obtained proved to be mixtures of diastereomers in contrast to the data.[5—8] Thus, the ^{1}H NMR spectrum of compound **5**, besides the signal for H(16) at δ 3.88 (dd, $^3J_{HH}$ = 10.6 and 4.7 Hz) of the predominant diastereomer, exhibits the corresponding signal at δ 4.87 (dd, $^3J_{HH}$ = 9.2 and 4.1 Hz) for the second diastereomer. The ratio of the integral intensities of the indicated signals allowed us to evaluate the diastereomeric proportion as ~6 : 1. The ^{1}H NMR spectra of the reduction products of halogenated derivatives **3** and **4**, besides diastereomers of compounds **7** and **8**, contain signals for the products of their dehalogenation, *viz.*, compounds **5** and **6**, respectively. However, compounds **5** and **6** are not predominant in the mixtures, as it has been indicated earlier.[8] The content of the dehalogenation products in both cases was ~25% (^{1}H NMR data), they can be easily separated from compounds **7** and **8** by chromatography. The content of the minor diastereomers in the case of compounds **7** and **8** was 22 and 18%, respectively. In the ^{1}H NMR spectrum of compound **7**, the signals H(16) and H(15) of the major diastereomer were found as doublets at δ 3.77 and 4.73 and $^3J_{HH}$ = 5.8 Hz, whereas the corresponding signals for the minor isomer had the patterns of a doublet and a doublet of doublets in the regions δ 3.97 ($^3J_{HH}$ = 3.8 Hz) and 4.29 ($^3J_{HH}$ = 3.7 Hz, $^4J_{HH}$ = 2.4 Hz), respectively. Comparing this spectrum with the spectrum of compound **1** (see Ref. 9), it can be suggested that the signal at δ 4.29 belongs to the atom H_α(15), and its constant $^4J_{HH}$ belongs to the interaction with the atom H_a(7) or H_a(14). The greater $^3J_{HH}$ constant for the more intensive signals allowed us to assign the predominant diastereomer to the compound with β-arrangement of the atom C(16)H, *i.e.*, the configuration of C(16) in it corresponded to that in the isosteviol hydroxy derivatives described earlier.[5—8] In the ^{1}H NMR spectrum of compound **8**, the signals for H(16) and H(15) were found as doublets of doublets in the regions δ 3.61 ($^3J_{HH}$ = 6.2, $^4J_{HH}$ = 1.0 Hz) and 4.86 ($^3J_{HH}$ = 6.2, $^4J_{HH}$ = 1.6 Hz) in the predominant diastereomer and as a doublet and a doublet of doublets at δ 4.20 ($^3J_{HH}$ = 4.2 Hz) and 4.33 ($^3J_{HH}$ = 4.0, $^4J_{HH}$ = 2.4 Hz) for the minor diastereomer.

The authors of the work[8] explained the stereospecificity of the reduction by steric hindrance created by the Me(17) group and the **C**-ring of compound **1**, which would have arisen with the β-arranged OH group. Introduction of the halogen atom at β-position at the atom C(15) makes the β-arrangement of the hydroxy group even more sterically hindered, however, this is the case when 16β-hydroxy diastereomer is formed in considerable amount. From our point of view, it would be more reasonable to interpret the stereospecificity of the reduction processes in compound **1** and its derivatives by smaller hindrance of the approach of the nucleophilic part of the pre-reaction complex $[BH_3—H]^-Na^+$ to the atom C(16) from under the plane of the five-membered ring from the side of the Me(17) group.[7]

The reaction of compounds **5**—**8** with the equimolar amounts of diethyl chlorophosphite and pyridine in benzene leads to the corresponding full esters of tervalent tricoordinated phosphorus, which is indicated by the presence in the ^{31}P NMR spectra of the reaction mixtures of signals in the region δ ~140. In the case of phosphorylation of compound **6** represented by a single diastereomer, the spectrum exhibited one signal in this region at δ 139.05. In the cases of compounds **5**, **7**, and **8**, existing as mixtures of two diastereomers with different configuration at the atom C(16), the spectrum exhibited two signals each with the ratio of integral intensities corresponding to the ratio of diastereomers in the starting compounds.

Upon prolonged storage in air or upon treatment of the reaction mixtures with water, the intermediate products of phosphorylation of **10** completely were converted to hydrophosphoryl compounds **11**—**14**. Compounds **11** and **13** were also obtained by dissolution of compounds **5** and **7** in a three-fold excess of diethyl chlorophosphite with addition of pyridine to the reaction mixtures and subsequent treatment with water.

Spectral characteristics (^{31}P and ^{1}H NMR) of compound **12** indicated the presence of a single diastereomer, *i.e.*, the phosphorylation and hydrolysis processes in this case have proved stereospecific. In the ^{31}P NMR spectrum of product **11**, two doublets at δ 8.47 (J_{PH} = 694.5 Hz) and 13.67 (J_{PH} = 670.0 Hz) were present with the ratio of integral intensities corresponding to the ratio of diastereomers in the starting compound **5**. It is obvious that the phosphorylation and hydrolysis in this case also proceeded stereospecifically, and the presence of the second diastereomer is explained by the diastereomeric composition of the starting compound **5**. The major diastereomer in the pure form was isolated after treatment of the product with hexane.

However, in the ^{31}P NMR spectrum of product **13** obtained by treatment of the mixture of diastereomers **7** with a three-fold excess of diethyl chlorophosphite, already four doublet signals at δ 7.36 (J_{PH} = 708.0 Hz, $^3J_{PH}$ = 8.4 Hz), 7.52 (J_{PH} = 703.3 Hz), 8.18 (J_{PH} = 699.0 Hz), 8.96 (J_{PH} = 718.1 Hz, $^3J_{PH}$ = 8.4 Hz) with the ratio of integral intensities 3.3 : 1 : 1 : 3.3 were observed. It is possible that these signals correspond to four diastereomers with differ-

ent configurations not only at the atom C(16), but also at the newly formed chiral center, *viz.*, at the phosphorus atom. The ^{1}H NMR spectrum of compound **13** also exhibits four downfield doublets at δ 6.90 (J_{HP} = 709.3 Hz), 6.95 (J_{HP} = 703.6 Hz), 6.97 (J_{HP} = 697.9 Hz), 7.06 (J_{HP} = 718.7 Hz) with the same ratio of integral intensities as for the previously indicated signals in the ^{31}P NMR spectrum. A mixture of epimers at the phosphorus atom with the ratio 1 : 1 and with *R*-configuration at the atom C(16) was isolated from the reaction mixture by column chromatography.

Four signals with the ratio of integral intensities 3 : 1 : 1 : 4 were observed in the ^{31}P NMR spectrum of compound **14**: δ 8.84 (J_{PH} = 713.1 Hz, $^3J_{PH}$ = 7.8 Hz), 9.00 (J_{PH} = 703.0 Hz), 9.72 (J_{PH} = 704.3 Hz), 10.05 (J_{PH} = 715.9 Hz, $^3J_{PH}$ = 6.9 Hz). The same ratio of integral intensities was also observed for the doublets of the protons at the phosphorus atom in the ^{1}H NMR spectrum: δ 6.94 (J_{HP} = 707.2 Hz), 6.97 (J_{HP} = 702.2 Hz), 6.99 (J_{HP} = 697.5 Hz), 7.13 (J_{HP} = 715.1 Hz). A mixture of the predominant epimers with R-configuration of C(16) in the ratio 1 : 1.3 remained upon decantation of the reaction product with hexane.

To sum up, the introduction of the halogen atom at 15β-position destroys the stereospecificity of phosphorylation and hydrolysis reactions.

The reaction of compounds **5** and **6** with phenyl dichlorophosphonite **9b** leads to a mixture of epimers. Thus, in the case of compound **5**, the ^{31}P NMR spectrum of the reaction mixture exhibits a singlet in the region δ 21.38 and four doublets in the regions δ 22.12, 22.91, 23.71, 25.13 with the ratio of integral intensities of the signals being 3 : 1 : 1 : 18 : 9, respectively. The doublets of low intensities belong apparently to the epimers at the phosphorus with *S*-configuration of the atom C(16) in product **15**, which are formed from the minor diastereomer of compound **5**. These signals disappeared when crystals isolated from the reaction mixture were washed with hexane. The singlet at δ 21.38 indicates partial oxidation of product **15** to compound **17**. Compound **17**, as well as a mixture of epimers (2 : 1) of compound **15** (*R*-configuration at the atom C(16)) was isolated by chromatography.

In the ^{31}P NMR spectrum of the reaction mixture obtained from methyl *ent*-16α-hydroxybeyeran-19-oate **6** and phenyl dichlorophosphonite **9b**, two doublets of equal intensities at δ 23.85 (J_{PH} = 563.4 Hz) and 25.44 (J_{PH} = = 571.2 Hz) were observed, which corresponded to two epimers at the phosphorus atom, as well as a singlet in the region δ 20.23 belonging, probably, to compound **18**, whose content in the mixture was ~30%. The latter, as well as a mixture of epimers (1 : 1) of compound **16** (*R*-configuration at C(16)) was isolated by chromatography.

In conclusion, we obtained new hydrophosphoryl compounds **11**—**16** based on compound **1** and studied their diastereomeric composition.

Experimental

IR spectra were recorded on a Bruker Vector-22 spectrometer in Nujol for crystals and between KBr plates for oils. ^{31}P NMR spectra were recorded on a Bruker CXP-100 spectrometer (36.48 MHz) in $CHCl_3$ using 85% H_3PO_4 as an external standard, ^{1}H NMR spectra were recorded on a Bruker Avance-600 spectrometer (600.13 MHz) in $CDCl_3$ using signals for the residual protons of deuterated chloroform as a reference. Angles of rotation were measured on a Perkin Elmer (Model 341) polarimeter at λ 589 nm (D-line of Na) and temperature 20 °C in $CHCl_3$. Specific rotations were calculated using the formula $[\alpha] = \alpha \cdot 100/c \cdot l$, where c is the concentration of the solution (g/100 mL), l is the pathway (dm), α is the measured rotation (deg), [α] is the specific rotation (deg mL(g dm)$^{-1}$). Melting points were measured on a Boetius heating stage.

Compounds **1**—**4** were synthesized according to the known procedures.[10—12]

***ent*-16-Hydroxybeyeran-19-oic acid (5).** Sodium borohydride (0.30 g, 7.0 mmol) was added to a solution of compound **1** (0.50 g, 1.6 mmol) in MeOH. The mixture was kept for 2 days at ~20 °C, quenched with 10% aqueous HCl, extracted with diethyl ether, dried with Na_2SO_4. The ether was evaporated to obtain a mixture of two diastereomers of compound **5**. Found (%): C, 75.09; H, 10.67. $C_{20}H_{32}O_3$. Calculated (%): C, 75.00; H, 10.18. ^{1}H NMR, δ: 0.68—2.15 (m, 29 H, protons of the beyerane framework and Me(20), Me(17), Me(18)); 3.88 (dd, 0.85 H, H_β(16), $^3J_{H_\beta H_\alpha}$ = 10.6 Hz, $^3J_{H_\beta H_\beta}$ = 4.7 Hz); 4.87 (dd, 0.15 H, H_α(16), $^3J_{H_\alpha H_\beta}$ = 9.2 Hz, $^3J_{H_\alpha H_\alpha}$ = 4.1 Hz).

Compounds **6**—**8** were obtained similarly.

Methyl *ent*-16α-hydroxybeyeran-19-oate (6) was obtained as a single diastereomer. Found (%): C, 75.83; H, 10.32. $C_{21}H_{34}O_3$. Calculated (%): C, 75.39; H, 10.26. ^{1}H NMR, δ: 0.73, 0.92, and 1.18 (all s, 3 H each, Me(20), Me(17), and Me(18)); 0.70—2.30 (m, 20 H, protons of the beyerane framework); 3.64 (s, 3 H, MeOOC); 3.87 (dd, 1 H, H_β(16), $^3J_{H_\beta H_\alpha}$ = = 10.5 Hz, $^3J_{H_\beta H_\beta}$ = 4.6 Hz).

***ent*-15β-Chloro-16-hydroxybeyeran-19-oic acid (7)** was obtained as a mixture of two diastereomers of compound **7** and a dechlorination product **5**. ^{1}H NMR of the reaction mixture, δ: 0.70—2.20 (m, protons of the beyerane framework and Me(20), Me(17), Me(18)); 3.77 and 4.73 (both d, 0.78 H each, H_β(16) and H_α(15), $^3J_{HH}$ = 5.8 Hz); 3.97 (d, 0.22 H, H_α(16), $^3J_{HH}$ = = 3.8 Hz); 4.29 (dd, 0.22 H, H_α(15), $^3J_{HH}$ = 3.7 Hz, $^4J_{HH}$ = 2.4 Hz); 3.88 (dd, 0.3 H, H_β(16) in dechlorination product **5**, $^3J_{H_\beta H_\alpha}$ = = 10.7 Hz, $^3J_{H_\beta H_\beta}$ = 4.8 Hz).

Compound **7** (0.32 g, 64%) was isolated after column chromatography (silica gel, eluent *n*-hexane : AcOEt, 1 : 1) as a mixture of diastereomers in the ratio 3.5 : 1 in total 64% yield. Found (%): C, 67.43; H, 8.87; Cl, 10.53. $C_{20}H_{31}ClO_3$. Calculated (%): C, 67.68; H, 8.80; Cl, 9.99.

Methyl *ent*-15β-bromo-16-hydroxybeyeran-19-oate (8) was obtained as a mixture of two diastereomers of compound **8** and a debromination product **6**. ^{1}H NMR of the reaction mixture, δ: 0.60—2.25 (protons of the beyerane framework and Me(20), Me(17), Me(18)); 3.61 and 4.86 (both dd, 0.82 H each, H_β(16) and H_α(15), $^3J_{HH}$ = 6.2 Hz, $^4J_{HH}$ = 1.0 Hz, $^4J_{HH}$ = 1.6 Hz); 4.20 (d, 0.18 H, H_α(16), $^3J_{HH}$ = 4.2 Hz); 4.33 (dd, 0.18 H, H_α(15), $^3J_{HH}$ = 4.0 Hz, $^4J_{HH}$ = 2.4 Hz); 3.66 and 3.64 (both s, 2.46 and 0.54 H, MeOOC in diastereomers); 3.87 (dd, 0.25 H, H_β(16) in debromination product **6**, $^3J_{H_\beta H_\alpha}$ =10.5 Hz, $^3J_{H_\beta H_\beta}$ = 4.6 Hz).

Compound **8** was isolated after chromatography (silica gel, eluent *n*-hexane : AcOEt, 3 : 1) as a mixture of diastereomers in the ratio 4.5 : 1 in total 68% yield. Found (%): C, 61.43; H, 8.21; Br, 19.08. $C_{21}H_{33}BrO_3$. Calculated (%): C, 61.01; H, 8.05; Br, 19.33.

***ent*-16-(Ethoxyhydrophosphoryloxy)beyeran-19-oic acid (11).** *ent*-16-Hydroxybeyeran-19-oic acid **5** (0.26 g, 0.8 mmol) was dissolved in diethyl chlorophosphite (0.33 g, 2.4 mmol), followed by addition of pyridine (0.06 g, 0.8 mmol). The reaction mixture was kept for 1 h, diluted with water. The separated dense mass was several times washed with water and dried in air. ^{31}P NMR, δ: 8.47 and 13.67 (both d, 0.85 and 0.15 P, J_{PH} = 694.5 Hz and J_{PH} = 670.0 Hz). Hexane was added. The crystals formed were filtered off and washed with hexane to obtain a predominant diastereomer (0.26 g, 78%) with m.p. 32 °C, [α] = –4 (*c* 0.10). Found (%): C, 64.43; H, 8.91; P, 7.08. $C_{22}H_{37}O_5P$. Calculated (%): C, 64.04; H, 9.06; P, 7.51. IR (ν/cm^{-1}): 971 (P—O—C), 1262 (P=O), 1715 (C=O), 2439 (P—H). ^{31}P NMR, δ: 8.47 (d, J_{PH} = 694.5 Hz). ^{1}H NMR, δ: 0.84, 0.98 and 1.24 (all s, 3 H each, Me(20), Me(17), Me(18)); 0.70—2.25 (m, 23 H, protons of the beyerane framework); 1.38 (t, 3 H, C<u>H</u>$_3$CH$_2$O, $^3J_{HH}$ = 7.1 Hz); 4.10—4.24 (m, 2 H, CH$_3$C<u>H</u>$_2$O); 4.44—4.54 (m, 1 H, H$_\beta$(16)); 6.86 (d, 1 H, HP, J_{HP} = 693.4 Hz).

Methyl *ent*-16α-(ethoxyhydrophosphoryloxy)beyeran-19-oate (12). Compound **6** (0.10 g, 0.3 mmol) was dissolved in anhydrous benzene (5 mL), diethyl chlorophosphite (0.04 g, 0.3 mmol) and pyridine (0.02 g, 0.3 mmol) were added. The mixture was stirred for 6 h under argon. A precipitate of Py · HCl was filtered off, benzene was evaporated from the filtrate. The residue was treated with water and extracted with diethyl ether. The extract was dried with Na_2SO_4. Compound **12** (0.1 g, 92%) was obtained after evaporation of ether as a dense oily mass, [α] = –45 (*c* 1.71). Found (%): C, 64.76; H, 9.63; P, 7.00. $C_{23}H_{39}O_5P$. Calculated (%): C, 64.75; H, 9.23; P, 7.26. IR (ν/cm^{-1}): 969 (P—O—C), 1260 (P=O), 1725 (C=O), 2426 (P—H). ^{31}P NMR, δ: 7.83 (d, J_{PH} = 690.3 Hz). ^{1}H NMR, δ: 0.65, 0.90 and 1.09 (all s, 3 H each, Me(20), Me(17), and Me(18)); 0.65—2.20 (m, 23 H, protons of the beyerane framework); 1.29 (t, 3 H, C<u>H</u>$_3$CH$_2$O, $^3J_{HH}$ = 7.0 Hz); 3.55 (s, 3 H, MeOOC); 4.00—4.15 (m, 2 H, CH$_3$C<u>H</u>$_2$O); 4.82—4.95 (m, 1 H, H$_\beta$(16)); 6.74 (dd, 1 H, HP, J_{HP} = 691.6 Hz, $^3J_{HH}$ = 5.2 Hz).

***ent*-15β-Chloro-16-(ethoxyhydrophosphoryloxy)beyeran-19-oic acid (13)** was obtained similarly to **11** from a mixture of diastereomers **7** (3.5 : 1). ^{31}P NMR of the reaction mixture, δ: 7.36 and 8.96 (both dd, 0.8 P each, J_{PH} = 708.0 Hz, $^3J_{PH}$ = 8.4 Hz, and J_{PH} = 718.1 Hz, $^3J_{PH}$ = 8.4 Hz); 7.52 and 8.12 (both d, 0.2 P each, J_{PH} = 703.3 Hz and J_{PH} = 699.0 Hz). This mixture was subjected to column chromatography (silica gel, eluent light petroleum (70—100 °C) : Et$_2$O, 1 : 1). The product **13** (a mixture of epimers at the P atom, 1 : 1) was obtained as clear low-melting crystals. The yield was 63%. Found (%): C, 59.02; H, 8.09; P, 7.00; Cl, 7.58. $C_{22}H_{36}O_5PCl$. Calculated (%): C, 59.11; H, 8.13; P, 6.93; Cl, 7.93. ^{31}P NMR, δ: 7.36 and 8.96 (both dd, 0.5 P each, J_{PH} = 708.0 Hz, $^3J_{PH}$ = 8.4 Hz, and J_{PH} = 718.1 Hz, $^3J_{PH}$ = 8.4 Hz). ^{1}H NMR, δ: 0.70—2.30 (30 H, protons of the beyerane framework, Me(20), Me(17), Me(18), and C<u>H</u>$_3$CH$_2$O); 3.60—3.90 and 4.50—4.65 (both m, 1 H each, H$_\beta$(16) and H$_\alpha$(15)); 4.10—4.40 (m, 2 H, CH$_3$C<u>H</u>$_2$O); 6.90 and 7.05 (both d, 0.5 H each, HP, J_{HP} = 710.0 Hz and J_{HP} = 718.9 Hz).

Methyl *ent*-15β-bromo-16-(ethoxyhydrophosphoryloxy)beyeran-19-oate (14) was obtained similarly to compound **13**. ^{31}P NMR, δ: 8.84 and 10.05 (both dd, 0.33 P and 0.11 P, J_{PH} = = 708.0 Hz, $^3J_{PH}$ = 8.4 Hz and J_{PH} = 718.1 Hz, $^3J_{PH}$ = 8.4 Hz); 9.00 and 9.72 (both d, 0.11 and 0.45 P, J_{PH} = 703.0 Hz and J_{PH} = 704.3 Hz). After hexane was decanted, the residue contained the product **14** (a mixture of epimers at the P atom, 1 : 1.3) as a dense oily mass. The yield was 68%. Found (%): C, 54.89; H, 8.01; Br, 16.03; P, 6.13. $C_{23}H_{38}BrO_5P$. Calculated (%): C, 54.65; H, 7.59; Br, 15.81; P, 6.13. ^{31}P NMR, δ: 8.84 and 10.05 (both dd, 0.43 P and 0.57 P, J_{PH} = 708.0 Hz, $^3J_{PH}$ = 8.4 Hz and J_{PH} = 718.1 Hz, $^3J_{PH}$ = 8.4 Hz). ^{1}H NMR, δ: 0.70—2.30 (33 H, protons of the beyerane framework, Me(20), Me(17), Me(18), and C<u>H</u>$_3$CH$_2$O); 3.66 (s, 3 H, MeOOC); 4.08—4.35 (m, 2 H, CH$_3$C<u>H</u>$_2$O); 4.40—4.60 (m, 1 H, H$_\beta$(16)); 4.72 (d, 1 H, H$_\alpha$(15), $^3J_{HH}$ = 6.4 Hz); 6.94 and 7.13 (both d, 0.44 and 0.56 H each, HP, J_{HP} = 707.2 Hz, J_{HP} = 715.1 Hz).

***ent*-16α-(Phenylhydrophosphoryloxy)beyeran-19-oic acid (15) and *ent*-16α-(phenylhydroxyphosphoryloxy)beyeran-19-oic acid (17).** Acid **5** (0.10 g, 0.3 mmol) was dissolved in anhydrous benzene (5 mL), followed by addition of $PhPCl_2$ (**9b**) (0.05 g, 0.3 mmol) and pyridine (0.02 g, 0.3 mmol). The mixture was stirred for 6 h under argon, washed with water, extracted with benzene. The extract was dried with Na_2SO_4, benzene was evaporated. After washing the residue with hexane and decantation, a dense oily mass (0.15 g) was obtained (^{31}P NMR, δ: 21.38 (s, compound **17**); 23.71 and 25.13 (both d, J_{PH} = 572.2 Hz and J_{PH} = 554.6 Hz), the ratio of integral intensities of the signals was 1 : 6 : 3), which was subjected to column chromatography (silica gel, eluent light petroleum (70—100 °C) : AcOEt, 5 : 2) to obtain compound **15** (0.09 g, 67%) (a mixture of epimers at the P atom, 2 : 1) as clear low-melting crystals and compound **17** (0.01 g, 7%). <u>Compound **15**</u>. Found (%): C, 70.20; H, 8.12; P, 7.02. $C_{26}H_{37}O_4P$. Calculated (%): C, 70.23; H, 8.41; P, 6.97. ^{31}P NMR, δ: 23.71 and 25.13 (both d, 0.66 P and 0.34 P). ^{1}H NMR, δ: 0.70—2.30 (29 H, protons of the beyerane framework and Me(20), Me(17), Me(18)); 4.38—4.51 (m, 1 H, H$_\beta$(16)); 7.61 (d, 1 H, HP, J_{HP} = 562.9 HZ); 7.35—7.95 (m, 5 H, Ph). <u>Compound **17**</u>. White crystals. M.p. 140—141 °C, [α] = –45 (*c* 0.37). Found (%): C, 67.03; H, 8.11; P, 6.72. $C_{26}H_{37}O_5P$. Calculated (%): C, 67.79; H, 8.11; P, 6.72. IR (ν/cm^{-1}): 974, 1045 (P—O—C), 1172 (P=O), 1697 (C=O). ^{31}P NMR, δ: 21.38 (s). ^{1}H NMR, δ: 0.75, 0.84 and 1.22 (all s, 3 H each, Me(20), Me(17), Me(18)); 0.5—2.2 (m, 20 H, protons of the beyerane framework); 3.96—4.04 (m, 1 H, H$_\beta$(16)); 7.35—7.90 (m, 5 H, Ph).

Methyl *ent*-16α-(phenylhydrophosphoryloxy)beyeran-19-oate (16) and methyl *ent*-16α-(phenylhydroxyphosphoryloxy)beyeran-19-oate (18) were obtained similarly to compounds **15** and **17**. <u>Compound **16**</u> (a mixture of epimers at the P atom, 1 : 1) was obtained as clear low-melting crystals. The yield was 60%. Found (%): C, 70.01; H, 8.35; P, 7.02. $C_{27}H_{39}O_4P$. Calculated (%): C, 70.70; H, 8.59; P, 6.75. ^{31}P NMR, δ: 23.85 and 25.84 (both d, 0.5 P each, J_{PH} = 563.4 Hz, J_{PH} = 571.2 Hz). ^{1}H NMR, δ: 0.54, 0.65, 0.76, 0.93, 1.05 and 1.07 (all s, 1.5 H each, Me(20), Me(17), and Me(18) in two epimers); 0.55—2.25 (m, 20 H, protons of the beyerane framework); 3.51 and 3.53 (both s, 1.5 H each, MeOOC in two epimer); 4.37—4.50 (m, 1 H, H$_\beta$(16)); 7.51 (d, 1 H, HP, J_{HP} = 563.1 Hz); 7.25—7.80 (m, 5 H, Ph). <u>Compound **18**</u>. White crystals, m.p. 161 °C, [α] = –49 (*c* 0.35). The yield was 16%. Found (%): C, 68.79; H, 8.09; P, 6.01. $C_{27}H_{39}O_5P$. Calculated (%): C, 68.32; H, 8.30; P, 6.53. IR (ν/cm^{-1}): 1007 (P—O—C), 1212 (P=O), 1724 (C=O). ^{31}P NMR, δ: 20.23 (s). ^{1}H NMR, δ: 0.67, 0.90 and 1.22 (all s, 3 H each,

Me(20), Me(17), and Me(18)); 0.50—2.20 (m, 20 H, protons of the beyerane framework); 3.62 (s, 3 H, MeOOC); 4.35—4.50 (m, 1 H, $H_\beta(16)$); 7.25—7.90 (m, 5 H, Ph).

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