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The Phosphonate-Phosphate and Phosphate-Phosphonate Rearrangement and Their Applications V [1]. On the Reaction of *s*-Butyllithium/*TMEDA* with Symmetrical Trialkyl Phosphates

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Summary. 1-(Tributylstannyl)hexanol ((±)-**8**) is phosphorylated to give phosphate (±)-**9** which is then transmetallated. The organolithium intermediate (±)-**10** isomerizes to α-hydroxyphosphonate (±)-**12**. Similar intermediates are also formed upon direct deprotonation of triethyl, tri-*n*-propyl, and tri-*n*-butyl phosphate, which subsequently rearrange to α-hydroxyphosphonates (±)-**14a–c**.

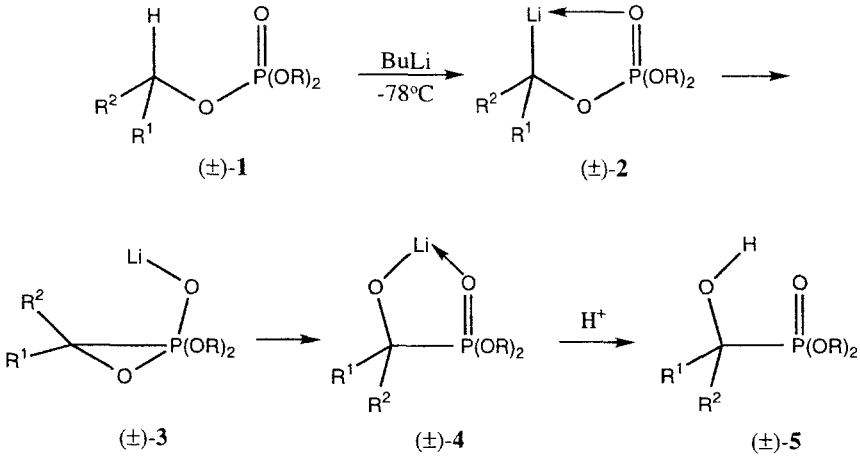
Keywords. α-Hydroxyphosphonates; Phosphates; Phosphate-phosphonate rearrangement; *s*-BuLi/*TMEDA*.

Die Phosphat-Phosphonat- und Phosphonat-Phosphat-Umlagerung und ihre Anwendungen, 5. Mitt. [1]. Über die Reaktion von *s*-Butyllithium/*TMEDA* mit symmetrischen Trialkylphosphaten

Zusammenfassung. 1-(Tributylstannyl)hexanol ((±)-**8**) wird phosphoryliert und liefert Phosphat (±)-**9**, das transmetalliert wird. Das lithiumorganische Zwischenprodukt (±)-**10** isomerisiert zum α-Hydroxyphosphonat (±)-**12**. Ähnliche Intermediate werden auch bei der direkten Deprotonierung von Triethyl-, Tri-*n*-propyl- und Tri-*n*-butylphosphat gebildet, die anschließend zu den α-Hydroxyphosphonaten (±)-**14a–c** umlagern.

Introduction

Hetero atom substituted carbanions [2, 3], their configurational stability, their reactions with electrophiles, and the stereochemistry of the substitution process have attracted much attention during the last years. The phosphate-phosphonate rearrangement [4] is an isomerization reaction with intermediate dipole-stabilized carbanions [5] (Scheme 1). They are formed by deprotonation of phosphoric acid esters (±)-1 with strong bases such as *s*-BuLi, *n*-BuLi, or *LDA*, if at least one of the substitutents R^1 or R^2 is electron withdrawing. An aryl [1, 4], a vinyl [6], or an alkinyl [7] group are sufficiently activating to enable the removal of the respective



Scheme 1

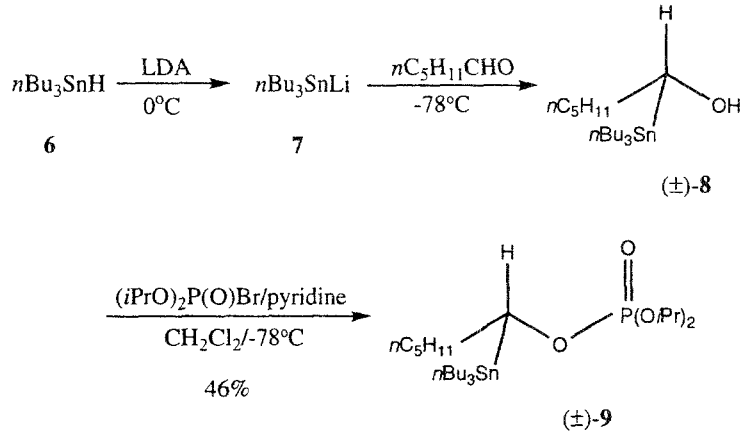
benzylic, allylic, or propargylic proton, either secondary or tertiary. The lithium complexed carbanion (±)-**2** forming a five-membered chelate ring is configurationally stable for the short livetime as proven for benzylic carbanions [8]. It is probably immediately intramolecularly phosphorylated *via* oxaphosphirane (±)-**3** to give finally phosphonate (±)-**4** and α-hydroxyphosphonate (±)-**5** upon workup. This sequence allows the base induced isomerization of phosphates to α-hydroxyphosphonates. The reverse process, the phosphonate-phosphate rearrangement (5 → 1) is well documented and follows the same mechanism [9]. Compound (±)-**2** is a member of lithium complexed α-oxycarbanions, of which the α-lithiated carbamates discovered by *Hoppe et al.* are the most important ones [2].

Results and Discussion

A phosphate can in principle react in three different ways with an alkyllithium compound: substitution at phosphorus with formation of a phosphonate (phosphorylation), elimination with formation of an olefin (E_2), and deprotonation in α position to the oxygen followed by isomerization (phosphate-phosphonate rearrangement). The first pathway has been used to prepare α-substituted phosphonates [10]: symmetrical trialkyl phosphates (ethyl, *n*-propyl, *n*-butyl, isopropyl, isobutyl) in solvent mixtures (*THF*/diethyl ether or *THF*/hexane) were treated with two equivalents of both linear or branched alkyllithium compounds at −78°C. Upon warming to 0°C, the phosphonates formed by substitution were deprotonated by an excess alkyllithium. The carbanions formed were reacted with a variety of electrophiles. No products formed by the phosphate-phosphonate rearrangement were detected using either *n*-BuLi or *n*-BuLi/*TMEDA* for the substitution process.

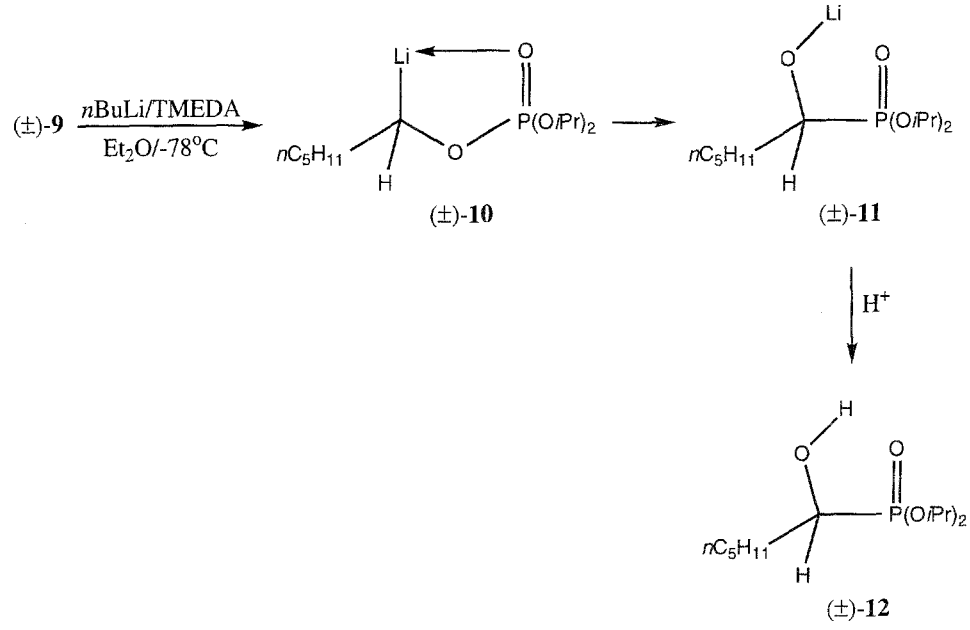
This paper focuses on the generation of carbanions of type (±)-**2** where R^1 is an ordinary alkyl group and R^2 = H. The major consequence of this is an increase in the basicity of the hydrogen which has to be abstracted relative to the acidity with activating substituents. As the result of *Savignac et al.* [10] for a direct deprotonation of phosphates were not encouraging, we decided to study the

feasibility to prepare a phosphoryloxy substituted carbanion derived from a trialkyl phosphate by tin-lithium exchange (Scheme 2). Hexanol was added to a solution of tributyltinlithium (7) prepared by deprotonation of tributyltinhydride with *LDA* by



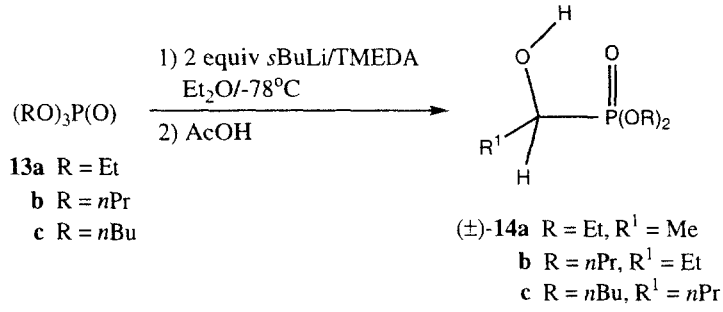
Scheme 2

the method of *Still* to give α-hydroxystannane (±)-**8** [11]. As α-hydroxystannanes are labile compounds, the crude product was not purified but immediately phosphorylated using bromo diisopropyl phosphate generated *in situ* from triisopropyl phosphite and bromine at −78°C. The crude product was purified by flash chromatography to afford diisopropyl phosphate (±)-**9** as a colourless oil in 46% yield. The isopropyl group was selected to increase the steric hindrance for substitution at phosphorus. Stannane (±)-**9** was treated with an excess of *n*-BuLi (1.5 equiv.) and a stoichiometric amount of *TMEDA* in diethyl ether at −78°C (Scheme 3). After 15 min, a sample was withdrawn for TLC. A single product had



Scheme 3

been formed, and stannane (±)-**9** was no longer present. After a total of 30 min, the reaction was quenched with acetic acid and worked up extractively to give the desired α-hydroxyphosphonate (±)-**12** after flash chromatography, being identical with an authentic sample. The high yield of 87% indicates that transmetallation is evidently a clean and rapid process to generate an α-phosphoryloxy substituted organolithium compound which rearranges instantaneously. This result provides strong evidence for the formation of intermediate (±)-**10** bearing only a *n*-pentyl group and not an activating substitutent. This method for the synthesis of α-hydroxyphosphonates is not very attractive as they can be generated much more easily by base catalyzed addition of phosphites to aldehydes (*Abramov* reaction [12]). The synthesis from phosphates would have great potential, especially if it were possible to generate the intermediate carbanion enantioselectively. Therefore, we studied the direct deprotonation of symmetrical phosphates derived from primary alcohols. The respective α-hydrogens of phosphates of primary alcohols should be more acidic than those of secondary ones.



Scheme 4

The first phosphate investigated was triethyl phosphate (**13a**, Scheme 4). 1 mmol of it was treated with 2 equiv. of *s*-BuLi/*TMEDA* in dry diethyl ether at −78°C, conditions ideally suited for the rearrangement of secondary benzylic phosphates. Excess acetic was added after 3 h to stop the reaction. Workup gave only 90 mg of crude product containing the desired α-hydroxyphosphonate (±)-**14a**. The low yield can at least in part be attributed to the low recovery during extractive workup because of its high polarity. On repetition of the experiment, only 1 ml of water was added to the concentrated reaction mixture which was extracted twice with ethyl acetate. A ^{31}P NMR spectrum was recorded of the crude product. The ratio of unreacted phosphate **13a** ($\delta = -0.23$ ppm) to α-hydroxyphophonate (±)-**14a** ($\delta = 26.59$ ppm) was 2:98. Flash chromatography gave α-hydroxyethylphosphonate (±)-**14a** in 41% yield. Similarly, tri-*n*-propyl phosphate (**13b**) was rearranged in diethyl ether with two equivalents of *s*-BuLi/*TMEDA*, extracted with dichloromethane, and purified to give α-hydroxyphosphonate (±)-**14b** in 66% yield (ratio of **13b**: (±)-**14b** = 2:98 in the crude product). Analogously, tri-*n*-butyl phosphate (**13c**) furnished the isomeric phosphonate (±)-**14c** in 53% yield. 30% of starting material (33% by ^1H NMR of the crude product) was recovered. When – after a reaction time of 3 h with 2 equiv. of *s*-BuLi/*TMEDA* – 0.8 mmol of *s*-BuLi were added and the mixture was stirred for another 3 h and

worked up, the yield decreased to 44%, although all starting material was consumed (^{31}P NMR). The best result in terms of yield (55%) was obtained when the reaction with (±)-**13c** was carried out in *THF* as solvent. No starting phosphate could be detected by ^{31}P NMR spectroscopy in the crude product. All ^{31}P NMR spectra of the crude products (±)-**14a–c** showed minor amounts of some impurities of unknown structure with phosphorus resonances between 35 and 60 ppm.

These results clearly indicate that simple phosphates derived from primary alcohols can be deprotonated in diethyl ether or *THF* at −78°C using *s*-BuLi in combination with *TMEDA* [13] to give phosphoryloxy substituted carbanions which probably isomerize immediately to α-hydroxyphosphonates. Surprisingly, substitution of RO^- by *s*-Bu^- is, if at all, of no significance, although the phosphorus is not shielded by bulky substituents. Possibly, the lone pairs at the four oxygen atoms bound to phosphorus inhibit the nucleophilic attack of *s*-Bu^- at phosphorus. We assume that the first reaction step is the complexation of lithium to the oxygen of the P=O function, thus inductively increasing the acidity of the hydrogens at the carbon α to oxygen. The strong complexation of Li^+ to *HMPTA* is well known and used in reactions with organolithium compounds to generate naked anions [15]. Furthermore, the fixation of lithium will direct the attacking *s*-Bu^- to the α-hydrogens (deprotonation) and not to the β-hydrogens (E_2 elimination, complex induced proximity effect [14]). The acidity of the α-hydrogens in these phosphates is remarkable and comparable, or even better, to the acidity of α-hydrogens in carbamates introduced by *Hoppe et al.* [16]. The results with other substrates will be published separately.

Experimental

TLC: Merck precoated TLC plates (0.25 mm), silica gel 60, F_{254}; detection: dipping the TLC plates into a solution of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (23 g) and $Ce(SO_4)_2\cdot 4H_2O$ (1 g) in 10% H_2SO_4 (500 ml) in water, followed by heating with a hot gun (α-hydroxyphosphonates are much more sensitive than phosphates). A second plate was sprayed with distilled water to detect phosphates. ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded with a Bruker AM 400 WB NMR spectrometer at 400.13, 100.61, and 161.97 MHz in $CDCl_3$; internal standard *TMS*, external standard H_3PO_4 (85%). In order to obtain undistorted ^{31}P signal intensities for an accurate integration, adequate relaxation times were used without irradiation during this period to avoid NOE enhancements. IR spectra were measured with a Perkin-Elmer 1600 FT-IR spectrometer. The samples were dissolved in CH_2Cl_2 and applied to a silicon plate [17]. The solvent was allowed to evaporate before recording the IR spectra. Flash chromatography: Merck silica gel 60, 0.040–0.063 mm; eluents: hexane, ethyl acetate, and dichloromethane. Reactions were carried out in dry solvents under argon. *THF* was distilled from potassium and diethyl ether from lithium aluminium hydride. *TMEDA* was refluxed for 5 h with CaH_2, distilled, and stored over molecular sieve (4 Å). Phosphates (99%, Aldrich) were used as supplied.

(±)-*Diisopropyl 1-(tributylstannyl)hexyl phosphate* ((±)-**9**)

The α-hydroxystannane (±)-**8** was prepared on a 10 mmol scale according to the general procedure for the synthesis of α-alkoxystannanes reported by *Still* [11]. The crude product was taken up in a mixture of dry CH_2Cl_2 (10 ml) and dry pyridine (1.6 ml) and added dropwise to a solution of bromo diisopropyl phosphate [1] at −50°C (see below). After stirring for 1 h at room temperature, water

(40 ml) was added. Stirring was continued for 30 min. The organic phase was separated and extracted with 2*N* HCl (30 ml). The combined aqueous layers were extracted twice with CH_2Cl_2. The combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo*. The product was purified by flash chromatography (hexane/CH_2Cl_2, 10:1) to yield (±)-**8** (2.51 g, 46%) as a colourless oil.

Preparation of bromo diisopropyl phosphate: A solution of triisopropyl phosphite (2.4 g, 2.85 ml, 11.5 mmol) in dry CH_2Cl_2 (15 ml) was cooled to −50°C. After the dropwise addition of bromine (1.76 g, 0.57 ml, 11 mmol) in dry CH_2Cl_2 (10 ml), stirring was continued for 1 h.

R_f = 0.18 (hexane/ethyl acetate, 10:1); IR (Si): ν = 2957, 2926, 2872, 2855, 1465, 1385, 1376, 1260, 1001 cm^{-1}; ^1H NMR: δ = 0.88 (m, 18H), 1.29 (m, 24H), 1.49 (m, 6H), 1.89 (m, 2H, CH_2CH), 4.56 (m, 2H, $(CH_3)_2CHO$), 4.66 (m, 1H, CH(OP)Sn) ppm; ^{13}C NMR: δ = 9.37 (CH_2Sn, $^1J(^{117/119}Sn, C)$ = 320.1, 305.7 Hz), 13.62 ($CH_3(CH_2)_3Sn$), 13.97 ($CH_3(CH_2)_4CH(OP)Sn$), 22.54 ($CH_2CH_2CH(OP)Sn$), 23.63 (d, $(CH_3)_2CH$, J_{PC} = 5.4 Hz), 23.68 (d, $(CH_3)_2CH$, J_{PC} = 5.4 Hz), 23.74 (d, $(CH_3)_2CH$, J_{PC} = 5.4 Hz), 26.87 ($CH_3CH_2CH_2(CH_2)_2CH(OP)Sn$, $^4J(^{117/119}Sn, C)$ = 22.3 Hz), 27.44 (CH_2CH_2Sn, $^2J(^{117/119}Sn, C)$ = 56.8 Hz), 29.03 ($CH_2CH_2CH_2Sn$, $^3J(^{117/119}Sn, C)$ = 20.0 Hz), 31.69 ($CH_3CH_2(CH_2)_3CH(OP)Sn$), 36.07 (d, J_{PC} = 2.9 Hz, CH_2CHOP), 71.67 (d, J_{PC} = 5.4 Hz, $(CH_3)_2CHO$), 71.73 (d, J_{PC} = 5.7 Hz, $(CH_3)_2CHO$), 75.78 (d, J_{PC} = 11.3 Hz, OCHSn, $^1J(^{117/119}Sn, C)$ = 371.5, 354.6 Hz) ppm; $C_{24}H_{53}O_4PSn$ (555.38); calc.: C 51.90, H 9.62; found: C 52.23, H 9.10.

Diisopropyl 1-hydroxyhexylphosphonate ((±)-**12**)

A stirred solution of (±)-**8** (555 mg, 1 mmol) and *TMEDA* (0.174 g, 0.225 ml, 1.5 mmol) in dry diethyl ether (8 ml) was cooled to −78°C under argon. After the dropwise addition of a solution of *n*-BuLi in pentane (0.94 ml, 1.5 mmol, 1.6 *M*), stirring was continued for 30 minutes. The reaction was quenched with a solution of acetic acid in dry diethyl ether (3 ml, 6 mmol, 2 *M*). The cooling bath was removed, and the reaction mixture was concentrated on a rotary evaporator. The residue was taken up in water (25 ml), and the solution was extracted four times with CH_2Cl_2. The combined organic phases were washed with water, dried (Na_2SO_4), and concentrated *in vacuo*. The product was purified by flash chromatography to yield hydroxyphosphonate (±)-**12** (231 mg, 87%), as a viscous oil which is identical with an authentic sample [18].

General procedure for the phosphate-phosphonate rearrangement of phosphates **13a–c**

A stirred solution of phosphate **13** (1 mmol) and *TMEDA* (0.23 g, 0.30 ml, 2 mmol) in dry solvent (8 ml, diethyl ether or *THF*) was cooled to −78°C under argon. After the dropwise addition of a solution of *s*-BuLi in cyclohexane (2 mmol, nominally 1.3 *M* but titrated from time to time get the actual concentration of *s*-BuLi [19]), stirring was continued for 3 h. The reaction was quenched with a solution of acetic acid in dry diethyl ether (8 mmol, 4 ml, 2 *M*). The cooling bath was removed, and the solution was concentrated on a rotary evaporator. The residue was taken up in water (15 ml), and the solution was extracted four times with CH_2Cl_2. The combined organic phases were washed with water, dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was purified by flash chromatography to yield known α-hydroxyphosphonate (±)-**14** as a colourless oil.

Diethyl 1-hydroxyethylphosphonate ((±)-**14a**)

This α-hydroxyphosphonate was prepared according to the general procedure using diethyl ether as solvent. After concentration *in vacuo*, the residue was taken up in water (1 ml) and ethyl acetate (10 ml) and stirred vigorously for 5 min. The aqueous layer was extracted with ethyl acetate (2 × 10 ml). The combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo*. The

residue was purified by flash chromatography using ethyl acetate as eluent to give (±)-**14a** (81 mg, 41%) as a colourless oil [20].

$R_f = 0.20$ (ethyl acetate); IR (Si): $\nu = 3315, 2983, 2935, 1393, 1220, 1028, 967\ cm^{-1}$; ^1H NMR: $\delta = 1.308$ (t, $J = 6.9$ Hz, 6H, CH_3CH_2O), 1.314 (t, $J = 6.9$ Hz, 6H, CH_3CH_2O), 1.41 (dd, $J = 7.1$, 17.5 Hz, 3H CH_3CHP), 3.49 (br s, 1H, OH), 4.00 (dq, $J = 3.7$, 7.1 Hz, 1H, CHP), 4.14 (m, 4H, OCH_2) ppm; ^{31}P NMR: $\delta = 26.59$ ppm.

Dipropyl 1-hydroxypropylphosphonate ((±)-**14b**)

(±)-**14b** was prepared according to the general prodedure using diethyl ether as solvent. The crude product was purified by flash chromatography (CH_2Cl_2/ethyl acetate, 3:2) to give (±)-**14b** (148 mg, 66%) as a colourless oil [21].

$R_f = 0.22$ (CH_2Cl_2/ethyl acetate, 3:2); IR (Si): $\nu = 3314, 2968, 1464, 1392, 1213, 999\ cm^{-1}$; ^1H NMR: $\delta = 0.92$ (t, $J = 7.4$ Hz, 6H, $CH_3(CH_2)_2O$), 1.04 (t, $J = 7.4$ Hz, 3H, CH_3CH_2CHP), 1.73 (m, 6H, CH_2), 3.10 (br s, 1H, OH), 3.75 (dt, $J = 4.2$, 9.0 Hz, 1H, CHP), 4.01 (m, 4H, OCH_2) ppm; ^{31}P NMR: $\delta = 25.96$ ppm.

Dibutyl 1-hydroxybutylphosphonate ((±)-**14c**)

(±)-**14c** was prepared according to the general prodedure using *THF* or diethyl ether as solvent. The crude products were purified by flash chromatography (CH_2Cl_2/ethyl acetate, 3:2) to give (±)-**14b** (146 mg, 55% (*THF*), 141 mg, 53% (diethyl ether)) as a colourless oil [22].

$R_f = 0.31$ (CH_2Cl_2/ethyl acetate, 3:2); IR (Si): $\nu = 3301, 2961, 2874, 1466, 1224, 1028\ cm^{-1}$; ^1H NMR: $\delta = 0.87$ (t, $J = 7.4$ Hz, 6H, $CH_3(CH_2)_3O$), 0.88 (t, $J = 7.4$ Hz, 3H, $CH_3(CH_2)_2CHP$), 1.35 (m, 5H, CH_2), 1.61 (m, 7H, CH_2), 2.85 (br s, 1H, OH), 3.80 (dt, $J = 8.9$, 4.4 Hz, 1H, CHP), 4.03 (m, 4H, OCH_2) ppm; ^{31}P NMR: $\delta = 26.16$ ppm.

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