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# Direct esterification of phosphinic acids under microwave conditions: extension to the synthesis of thiophosphinates and new mechanistic insights

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ABSTRACT

The direct esterification of phosphinic acids has been extended to the preparation of thiophosphinates using thiols, but the conversions are only ca. 50%. The outcome is in agreement with the unexpectedly high enthalpy of activation and endothermicity suggested by quantum chemical calculations. At the same time, formation of the thiophosphinates confirms the $A_{AC}2$ (phosphinylation) mechanism and excludes the $S_N$ reaction paths. Formation of an olefinic intermediate under the reaction conditions is also excluded experimentally.

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It is well-known that phosphinic acids do not undergo esterification with alcohols under traditional thermal conditions. For this reason, phosphinates are usually prepared by the reaction of phosphinic chlorides with alcohols in the presence of a base.[1] We, however, found that the direct esterification of phosphinic acids is possible under microwave (MW) conditions[2,3] as a consequence of the beneficial effect of MW irradiation.[4] We assumed that the statistically occurring local overheating effect[4] can overcome the barrier corresponding to the high values of the enthalpy of activation (102–161 kJ $mol^{-1}$).[4] It was also found that the esterifications under discussion are virtually thermoneutral.[5] Quantum chemical calculations suggested that four-membered transition states (TSs) are involved in the rate-determining step of the esterifications and amidations.[5] The proposed mechanism for the esterification is shown in Scheme 1.

The theoretically possible mechanistic pathways leading to the phosphinic ester **5** are shown in general in Scheme 2.

Phosphinate **5** may be formed by acylation/phosphinylation of the alcohol (as shown by the '$A_{AC}2$' routes in red), or by alkylation of the phosphinic acid (**1**) (as shown by the '$S_N2$' and '$S_N1$' routes in green and blue, respectively). Considering the '$A_{AC}2$' protocol, the first step is the protonation of the phosphinic acid **1** (that is, autoprotonation in our case). Then, the alcohol attacks the electrophilic P=O moiety of the protonated phosphinic acid **2**. Envisaging an analogous mechanism to that for the esterification of carboxylic acids, this step is followed by proton transfer, converting intermediate **6** into **7**. Dehydration of species **7** leads to the protonated form of the phosphinate **4**. Scheme 1 also shows the '$A_{AC}2$' route suggested by quantum chemical calculations.[5] According to this, the protonated product **4** is formed via the above mentioned four-membered TS (**3**). The relevance of a cyclic TS in the phosphinylation mechanism theory is a novel discovery. But how is it possible to exclude the '$S_N2$' and '$S_N1$' mechanisms involving protonation of the alcohol (by the phosphinic acid) in the first step, which is followed by nucleophilic attack by the hydroxy group of the phosphinic acid on the α-carbon atom of the protonated alcohol to furnish the protonated phosphinate **9** via TS **8** ($S_N2$), or by dehydration and subsequent reaction of the cation ($RCH_2CH_2^+$) so formed with the phosphinic acid **1**? The result of the '$S_N1$' route is, of course, the same (species **9**, and after deprotonation, **5**).

To answer the above question, we studied the reaction of 3-phospholene 1-oxides **12** and **13** with thiols, such as 1-butanethiol and 1-pentanethiol under MW conditions. As in earlier cases, the thiols were applied in 14-fold excess and the reactions were accomplished at ca. 200–220°C over 4–8 h in sealed tubes.[6] It was a question of whether the esterification takes place, and if so, whether the monothiophosphinates **14**/**15**, or the phosphinates **16** are formed. It was found that the reaction had occurred in all cases with conversions of ca. 51%. The work-up procedure, comprising the removal of the volatile components followed by purification by chromatography, led to the monothiophosphinates **14**/**15**

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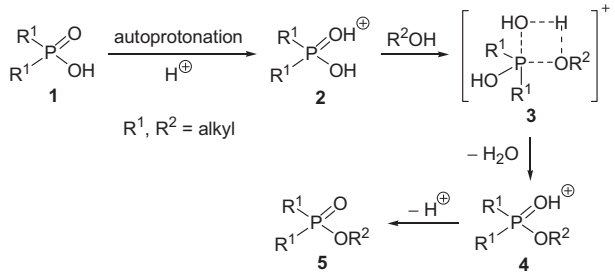
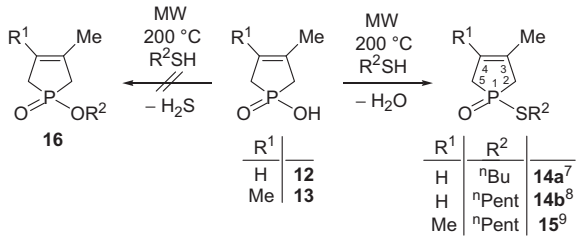



**Scheme 1.** Mechanism for the MW-assisted direct esterification of phosphinic acids.




**Scheme 3.** MW-assisted direct esterification of 1-hydroxy-3-phospholene 1-oxides with thiols.

in yields of 36–40%. No phosphinates **16** were formed (Scheme 3). The unreacted phosphinic acids **12** and **13** were recovered. Thiophosphinates **14a**,**b** and **15** were identified by $^{31}P$, $^{13}C$ and $^{1}H$ NMR spectroscopy, as well from mass spectral data.[7–9]

On conventional heating at 200°C for 6 h, the conversions of the reactions of phosphinic acid **12** with the thiols were below 10%.

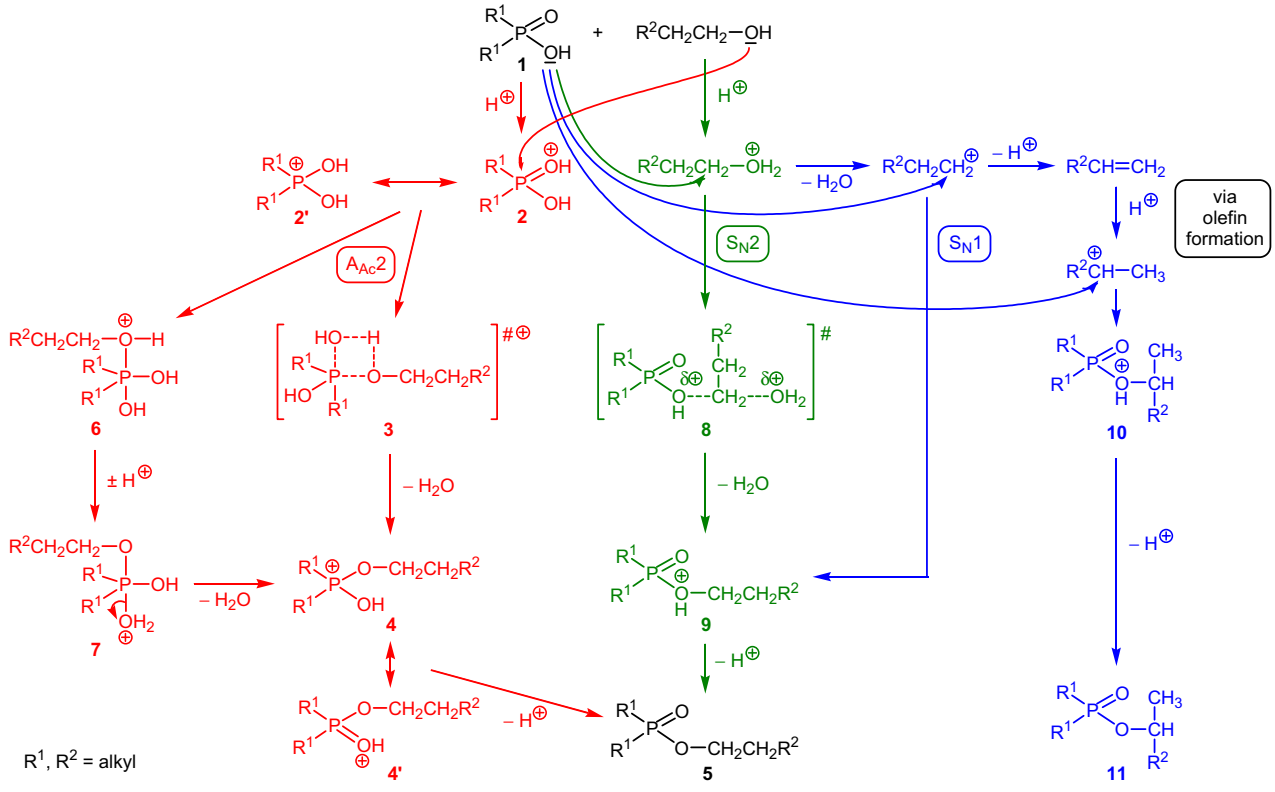
The 1-thioalkoxy-3-phospholene 1-oxides **14** and **15** can also be synthesized by the conventional approach via the 1-chloro-3-phospholene 1-oxides[10] prepared in a separate step from the corresponding phosphinic acids **12** and **13**. However, it is a disadvantage that, in this case, the thioesterification involves two steps.

On the one hand, our experiments on direct esterifications unambiguously justified the $A_{AC}2$ mechanism during the reaction of phosphinic acids and thiols. Accordingly, the thiol is phosphinylated by the cyclic phosphinic acid, meaning that the phosphinic acid is not alkylated by the thiol in an $S_N2$ or $S_N1$ mechanism. It follows that the phosphinylation (acylation) mechanism, which is obviously valid also for the reaction of phosphinic acids with alcohols, is supported by experimental proof. The incorporation of a sulfur atom instead of oxygen into the product somewhat resembles isotopic labeling.

On the other hand, the question arises as to why the conversions in the reactions of phosphinic acids **12** and **13** with thiols are incomplete? To answer this, B3LYP/6-31++G(d,p) calculations were carried out on the reaction of 1-hydroxy-3-methyl-3-phospholene 1-oxide (**12**) with thiobutanol, and as a comparison, also on the reaction of the same hydroxy-phospholene (**12**) with butanol. We wished to map the energetics of these reactions. The structures of the two respective TSs (**17** and **18**) together with selected geometries are shown in Figures 1 and 2.

It can be seen, that the O–>S exchange in the four-membered TS **17**/**18** is associated with a bond elongation of 28%, while the O–P–X (X = O and S) angle in the four-membered ring changes only slightly (71.7 vs 74.4 deg.) The energy diagrams for the **12** → **14a** and **12** → 1-butoxy-3-methyl-3-phospholene 1-oxide (**19**) transformations are shown in Figures 3 and 4, respectively.

It can be seen that the direct esterification of 1-hydroxy-3-phospholene oxide (**12**) with 1-butanethiol involves a significantly higher enthalpy of activation, than that with butanol ($\Delta H^{\#}$ = 145.4 vs 101.7 kJ mol$^{-1}$). It is also significant that while the reaction with




**Scheme 2.** Possible reaction paths for the formation of phosphinates.

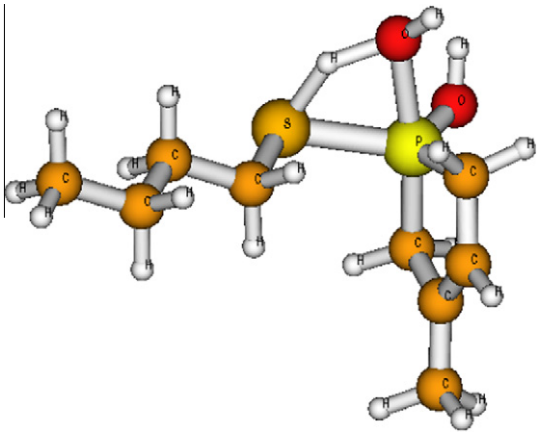


**Figure 1.** TS **17** for the esterification of 1-hydroxy-3-methyl-3-phospholene 1-oxide (**12**) and 1-butanethiol calculated by the B3LYP/6-31++G(d,p) method.[11] Selected geometries (bond distances, bond angles, and torsion angles) are given in Å and deg. P–S 2.278, P–O1 1.975, P–O2 1.614, P–C2 1.869, C2–C3 1.513, C3–C4 1.344, C4–C5 1.505, P–C5 1.849, S…H 1.469, O1…H 1.452, S–C1′ 1.867, C1′–C2′ 1.532, C2′–C3′ 1.541, C3′–C4′ 1.533, P–S…H 74.73, P–O1…H 85.75, P–C2–C3 105.33, C2–C3–C4 115.91, C3–C4–C5 118.47, C5–P–C2 94.13, S–P–O1 74.41, S–P–O2 115.41, P–S–C1′ 104.85, S–C1′–C2′ 109.47, C1′–C2′–C3′ 110.75, C2′–C3′–C4′ 112.12, O1–P–S…H −5.18, P–C2–C3–C4 −8.01, P–C2–C3–Me 173.83, C2–C3–C4–C5 1.11, C3–C4–C5–P 6.47, P–S–C1′–C2′ 165.22, S–C1′–C2′–C3′ 177.95, C1′–C2′–C3′–C4′ 179.56. (For the numbering of the five-membered hetero ring, see Scheme 3, in P(O1-H)O2-H, O1 is the ring O, while O2 is the exocyclic O, C1′–C2′–C3′–C4′ represent the atoms of the Bu group).

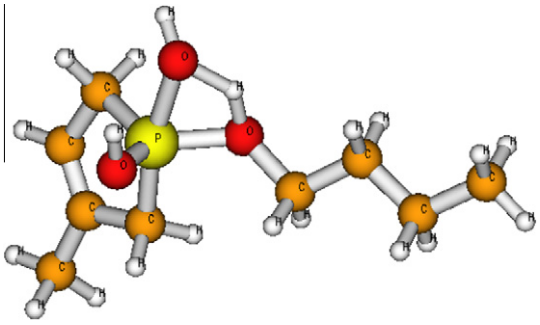


**Figure 2.** TS **18** for the esterification of 1-hydroxy-3-methyl-3-phospholene 1-oxide (**12**) and butanol calculated by the B3LYP/6-31++G(d,p) method.[11] Selected geometries (bond distances, bond angles, and torsion angles) are given in Å and deg. P–O 1.778, P–O1 1.947, P–O2 1.607, P–C2 1.853, C2–C3 1.518, C3–C4 1.343, C4–C5 1.506, P–C5 1.842, O…H 1.095, O1…H 1.371, O–C1′ 1.502, C1′–C2′ 1.517, C2′–C3′ 1.541, C3′–C4′ 1.533, P–O…H 88.88, P–O1…H 74.96, P–C2–C3 104.04, C2–C3–C4 115.81, C3–C4–C5 118.27, C4–C5–P 103.74, O–P–O1 71.69, O–P–O2 116.55, P–O–C1′ 127.94, O–C1′–C2′ 108.39, C1′–C2′–C3′ 110.79, C2′–C3′–C4′ 112.13, O1–P–O…H 1.43, P–C2–C3–C4 13.27, P–C2–C3–Me −167.41, C2–C3–C4–C5 −1.314, C3–C4–C5–P −11.43, P–O–C1′–C2′ −156.20, O–C1′–C2′–C3′ −177.94, C1′–C2′–C3′–C4′ −179.68. (For atom numbering see the caption to Fig. 1.).

thiobutanol is clearly endothermic ($\Delta H^0$ = 48.5 kJ mol$^{-1}$), that with butanol is only slightly so, being rather near to thermoneutral ($\Delta H^0$ = 3.3 kJ mol$^{-1}$). Our experience is that the beneficial effect of MW irradiation, that is the statistically occurring local overheating effect, may overcome the relatively high enthalpy of activation values,[4] but the endothermicity works against this positive impact leading eventually to incomplete conversions. Hence, the theory and practice (incomplete conversions) are in good agreement for the cases under discussion.

Returning to Scheme 2 showing the possible routes leading to phosphinate **5**: there is still a possibility that has not been mentioned. This is the route in which the protonated alcohol is converted into an olefin, $R^2CH{=}CH_2$, and this species acts as the alkylating agent after protonation. This approach would lead to

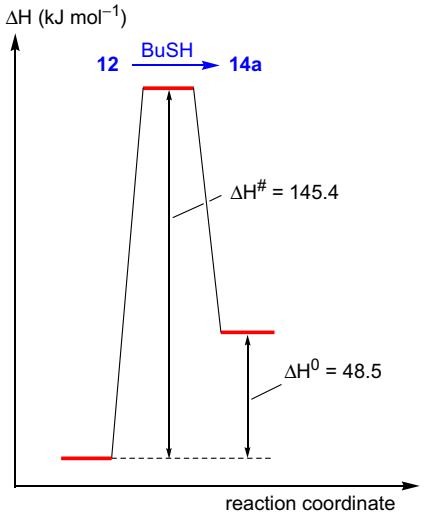



**Figure 3.** Enthalpy profile for the esterification of 1-hydroxy-3-phospholene oxide (**12**) with 1-butanethiol.

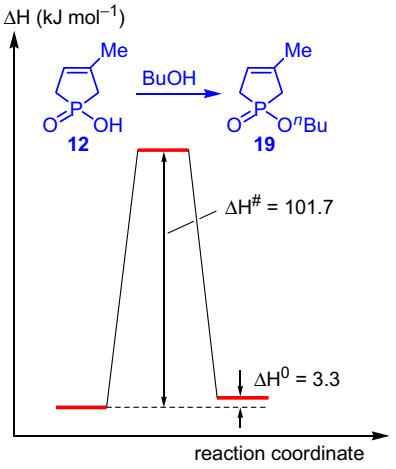
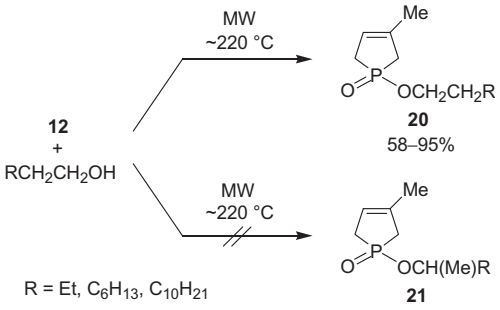


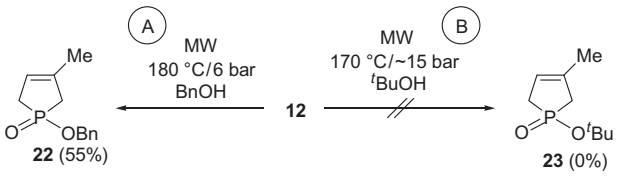

**Figure 4.** Enthalpy profile for the esterification of 1-hydroxy-3-phospholene oxide (**12**) with butanol.




**Scheme 4.** MW-assisted direct esterification of 1-hydroxy-3-phospholene 1-oxide (**12**) with various alcohols.

the ester with a branched alkyl group **21** according to the Markovnikov orientation. However, this route can be excluded, as only cyclic phosphinates with linear alkyl groups **20** were obtained.[3,5] A few examples are shown in Scheme 4.

Two additional experimental observations are also against the involvement of an olefin-type intermediate. Using benzyl alcohol




**Scheme 5.** MW-assisted direct esterification of 1-hydroxy-3-phospholene 1-oxide (**12**) with benzyl alcohol and *tert*-butanol.

as the reactant, the expected benzyl phosphinate **22**[12] was formed (Scheme 5A). At the same time, there was no reaction with *tert*-butanol (Scheme 5B).

The fact that the benzyl phosphinate **22** was formed is of principal importance in excluding the mechanism via olefin formation. The lack of the formation of the *tert*-butyl phosphinate **23** at a reaction temperature of 170°C confirms the lack of 2-methylprop-1-ene formation under such conditions, and at the same time shows that the phosphinylation cannot take place due to steric hindrance.

In conclusion, the MW-assisted direct esterification was extended to the synthesis of new cyclic monothiophosphinates. Formation of these products proved the phosphinylation mechanism and that the incomplete conversions could be explained by the calculated energetics.

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6. *General procedure for the direct thioesterification of 1-hydroxy-3-methyl-3-phospholene 1-oxide (**12**) under MW irradiation.*
   A mixture of 0.76 mmol of the phosphinic acid (0.1 g of **12**, 0.11 g of **13**) and 11.4 mmol of the thiol (1.2 mL of 1-butanethiol or 1.4 mL of 1-pentanethiol) in a sealed tube was irradiated in a 300 W CEM Discover focused MW reactor equipped with a pressure controller at 200°C for 6 h. (The reaction vessel was sealed under nitrogen. The pressure developed was in the range of 6–7 bar). The excess thiol was removed under reduced pressure, and the residue so obtained purified by flash column chromatography using silica gel and 3% MeOH in $CHCl_3$ as the eluant to afford phosphinate **14a**, **14b,** or **15** as oils. All operations with thiophosphinates were carried out under nitrogen.
7. *Compound **14a***: Yield: 38%; $^{31}P$ NMR (121.5 MHz, $CDCl_3$) $\delta$ 75.2; $^{13}C$ NMR (75.5 MHz, $CDCl_3$) $\delta$ 12.8 ($CH_2CH_3$), 19.6 ($^3J$ = 11.8, C3–$CH_3$), 21.0 ($CH_2CH_3$), 27.6 ($CH_2$), 32.6 ($SCH_2$), 36.7 ($^1J$ = 66.0, C2), 39.4 ($^1J$ = 69.1, C5), 119.5 ($^2J$ = 9.5, C4), 135.5 ($^2J$ = 15.1, C3); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.88 (t, $J$ = 7.3, 3H, $CH_2CH_3$), 1.31–1.47 (m, 2H, $CH_2CH_3$), 1.60–1.72 (m, 2H, $CH_2$), 1.76 (s, 3H, C3–$CH_3$), 2.45–2.83 (m, 4H, $PCH_2$), 2.83–2.96 (m, 2H, $SCH_2$), 5.48 (d, $J$ = 35.4, 1H, CH); $[M+H]^+_{found}$ = 205.0821, $C_9H_{18}OPS$ requires 205.0816.
8. *Compound **14b***: Yield: 40%; $^{31}P$ NMR (121.5 MHz, $CDCl_3$) $\delta$ 74.5; $^{13}C$ NMR (75.5 MHz, $CDCl_3$) $\delta$ 13.2 ($CH_2CH_3$), 19.6 ($^3J$ = 12.0, C3–$CH_3$), 21.4 ($CH_2CH_3$), 27.9 ($CH_2$), 30.1 ($SCH_2CH_2$), 30.2 ($^2J$ = 3.5, $SCH_2$), 36.7 ($^1J$ = 65.9, C2), 39.4 ($^1J$ = 69.1, C5), 119.5 ($^2J$ = 9.7, C4), 135.5 ($^2J$ = 15.2, C3); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.90 (t, $J$ = 7.0, 3H, $CH_2CH_3$), 1.25–1.47 (m, 4H, 2 $\times CH_2$), 1.64–1.77 (m, 2H, $SCH_2CH_2$), 1.82 (s, 3H, C3–$CH_3$), 2.50–2.88 (m, 4H, $PCH_2$), 2.88–3.02 (m, 2H, $SCH_2$), 5.53 (d, $J$ = 36.0, 1H, CH); $[M+H]^+_{found}$ = 219.0977, $C_{10}H_{20}OPS$ requires 219.0973.
9. *Compound **15***: Yield: 36%; $^{31}P$ NMR (121.5 MHz, $CDCl_3$) $\delta$ 67.5; $^{13}C$ NMR (75.5 MHz, $CDCl_3$) $\delta$ 13.7 ($CH_2CH_3$), 16.2 ($^3J$ = 12.0, C3–$CH_3$), 21.9 ($CH_2CH_3$), 28.4 ($^3J$ = 2.6, $SCH_2CH_2$), 30.6 ($CH_2$), 30.8 ($^2J$ = 3.9, $SCH_2$), 42.2 ($^1J$ = 68.1, C2), 127.1 ($^2J$ = 11.2, C3); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.82 (t, $J$ = 7.0, 3H, $CH_2CH_3$), 1.17–1.40 (m, 4H, 2$\times CH_2$), 1.59–1.73 (m, total intensity 8H, 2$\times$C3–$CH_3$, $CH_2$), 2.48–2.64 (m, 2H, $SCH_2$), 2.66–2.94 (m, 4H, $PCH_2$); $[M+H]^+_{found}$ = 233.1130, $C_{11}H_{22}OPS$ requires 233.1129.
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12. *Compound **22***: Yield: 55%; $^{31}P$ NMR (121.5 MHz, $CDCl_3$) $\delta$ 76.3; $^{13}C$ NMR (75.5 MHz, $CDCl_3$) $\delta$ 20.6 ($^3J$ = 13.0, C3–$CH_3$), 30.9 ($^1J$ = 87.6, C2), 33.5 ($^1J$ = 91.6, C5), 66.2 ($^2J$ = 6.4, $OCH_2$), 120.2 ($^2J$ = 11.0, C4), 127.8 (C2′), 128.3 (C4′), 128.5 (C3′), 136.1 ($^2J$ = 17.0, C3), 136.2 ($^3J$ = 5.5, C1′); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.75 (s, 3H, C3–$CH_3$), 2.22–2.53 (m, 4H, $PCH_2$), 5.08 (d, $J$ = 8.8, 2H, $OCH_2$), 5.49 (d, $J$ = 37.1, 1H, CH), 7.29–7.40 (m, 5H, $C_6H_5$); $[M+H]^+_{found}$ = 223.0883, $C_{12}H_{16}O_2P$ requires 223.0888.
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