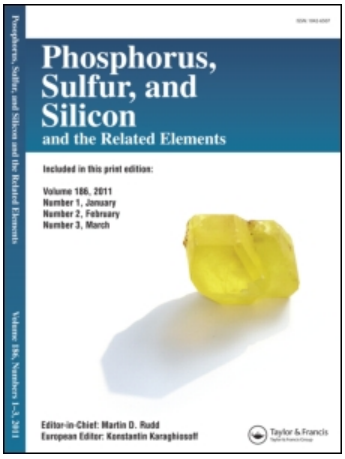

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THE PHOSPHATE-PHOSPHONATE AND PHOSPHONATE-PHOSPHATE REARRANGEMENTS AND THEIR APPLICATIONS - 7[1]: USE OF *t*-BUTYL AS PROTECTING GROUP AND SYNTHESIS OF CHIRAL, NONRACEMIC α-HYDROXYPHOSPHONATES

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THE PHOSPHATE-PHOSPHONATE AND PHOSPHONATE-PHOSPHATE REARRANGEMENTS AND THEIR APPLICATIONS – 7[1]: USE OF *t*-BUTYL AS PROTECTING GROUP AND SYNTHESIS OF CHIRAL, NONRACEMIC α-HYDROXYPHOSPHONATES

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The regioselectivity of metallation of hexyl diisopropyl phosphate (**1**) depends on the solvent, the temperature, and the base used. The best results are obtained with *s*-BuLi/TMEDA in hexane and diethyl ether at -78 °C, the CH_2O group being deprotonated preferentially over the CHO group (3:1 versus 2.5:1). The intermediate phosphonyloxy-substituted alkyllithiums (±)-**4** and (±)-**5** rearrange to phosphonates (±)-**6** and (±)-**7**, respectively. The isopropyl groups can be replaced by *t*-butyl groups to direct metallation exclusively to CH_2O. Homochiral diamines in place of TMEDA give chiral, nonracemic α-hydroxyphosphonates.

Keywords: metallation; α-hydroxyphosphonates; alkyllithiums; homochiral diamines; phosphates

INTRODUCTION

In the preceding paper, we demonstrated that the deprotonation of diisopropyl phosphates of primay aliphatic alcohols with *s*-BuLi/TMEDA occurs on the alkyl and isopropyl group.[1] The intermediate α-phosphonyloxy-substituted alkyllithiums are configurationally stable and isomerize with retention of configuration to secondary and tertiary

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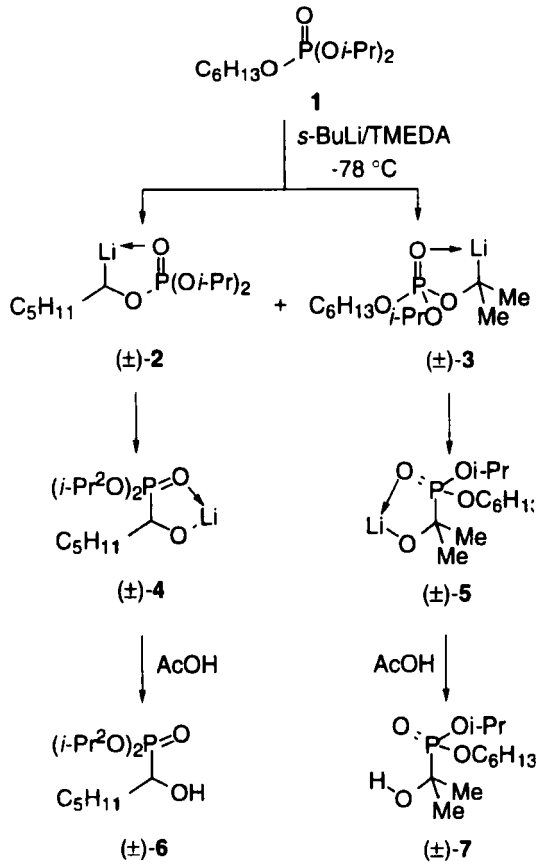
α-hydroxyphosphonates, respectively (phosphate-phosphonate rearrangement). If the two isopropyl groups of the phosphate are replaced by heptadeuterioisopropyl groups, the OCH_2 group of the previously primary alcohol is metallated exclusively, because of a high primary kinetic isotope effect. To improve the synthetic utility of the reaction for the preparation of α-hydroxyphosphonates, we investigated the influence of the reaction conditions on the regioselectivity of the proton abstraction, the use of some other protecting groups, and application of homochiral diamines for enantioselective metallations.

RESULTS AND DISCUSSION

Influence of Reaction Conditions on Regioselectivity of Deprotonation

For ease of comparison with previous results, hexyl diisopropyl phosphate (**1**)[11] was used as substrate for the phosphate-phosphonate rearrangement on a 1 mmol scale as reported to study the ratio of α-hydroxyphosphonates (±)-**6** and (±)-**7** formed by varying the reaction parameters, i. e. temperature, solvent, and base (Scheme 1, Table I).[11] This ratio reflects the extent of metallation at the methylene and methine group. The crude products obtained in diethyl ether und *n*-hexane as solvents at −78 °C with *s*-BuLi/TMEDA have virtually the same composition, with the secondary α-hydroxyphosphonate (±)-**6** predominating (Entries 1 and 2). The ratios of (±)-**6**:(±)-**7** are 2.5:1 and 3:1, respectively. In THF under otherwise identical conditions, the amount of the tertiary α-hydroxyphosphonate (±)-**7** increased [(±)-**6**:(±)-**7** = 1.5:1] (Entry 3). No tertiary α-hydroxyphosphonate was formed in diethyl ether at −94 °C and the reaction rate decreased dramatically relative to −78 °C so that the crude product contains 82% of starting phosphate **1** even after a reaction time of 8 h (Entry 4). In diethyl ether at −40 °C the reaction was finished in 2 h, but the tertiary α-hydroxyphosphonate predominated [(±)-**6**:(±)-**7** = 1.5:1] (Entry 5). Surprisingly, the phosphate-phosphonate rearrangement did not take place in DME at −40 °C (Entry 6). It might well be possible, that the lithium cation forms a much stronger complex with DME than with the P=O of the phosphate, which is probably necessary for metallation. Replacing *s*-BuLi by *t*-BuLi resulted in a significant drop in reaction rate

in *n*-hexane and diethyl ether and only the secondary α-hydroxyphosphonate was generated in a small amount (4%) (Entries 7 and 8). *n*-BuLi does not metallate phosphates, but affords butylphosphonates by substitution as found by Savignac and Teulade.[2]



SCHEME 1 Metallation and rearrangement of hexyl diisopropyl phosphate (1)

The best conditions for deprotonation of phosphates are *s*-BuLi/TMEDA in diethyl ether or *n*-hexane at −78 °C. The formation of the tertiary phosphonate could not be prevented, which caused us to test the *t*-butyl group as an alternative protecting group.

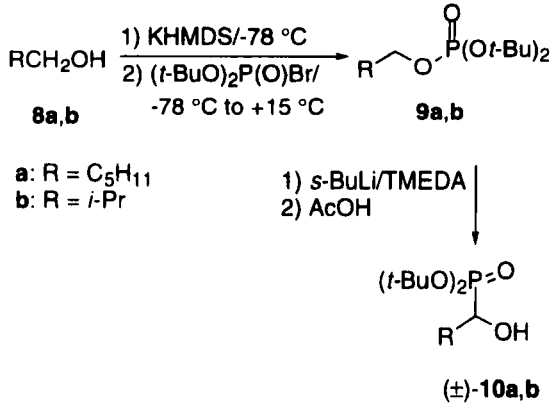
TABLE I Rearrangement of phosphate **1** under various conditions

Entry	*Base*[a]	*Solvent*	*Temp.*	*Time*	***1*** *(%)*[b]	***6*** *(%)*[b]	***7*** *(%)*[b]	***6:7***[b]
1	*s*-BuLi	Et_2O	−78 °C	3 h	6	67	27	2.5:1
2	*s*-BuLi	*n*-hexane	−78 °C	3 h	9	68	23	3:1
3	*s*-BuLi	THF	−78 °C	3 h	1	60	39	1.5:1
4	*s*-BuLi	Et_2O	−94 °C	8 h	82	18	0	0
5	*s*-BuLi	Et_2O	−40 °C	2 h	7	38	55	1:1.4
6	*s*-BuLi	DME	−50 °C	2 h	100	0	0	–
7	*t*-BuLi	Et_2O	−78 °C	3 h	96	4	0	–
8	*t*-BuLi	*n*-hexane	−78 °C	3 h	96	4	0	–

a. In combination with TMEDA.
b. Composition of crude product as determined by ^{31}P NMR spectroscopy.

Use of t-Butyl, Dimethylamino, and 2,2-Dimethylpropane-1,3-diyl as Protecting Groups at Phosphorus

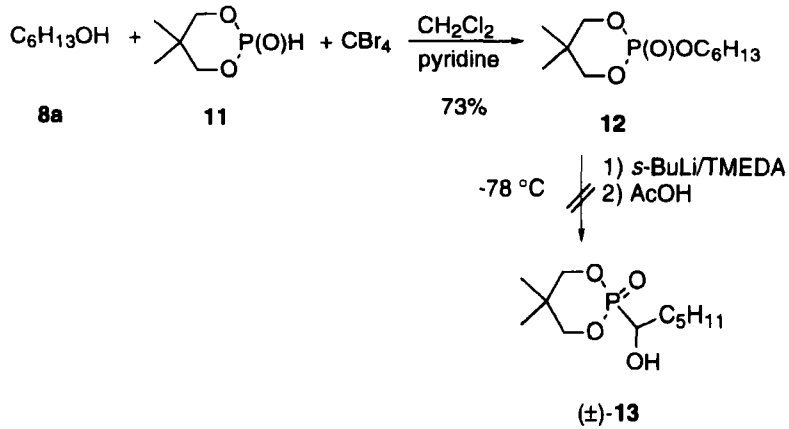
The *t*-butyl group on phosphorus is fairly labile under acidic conditions, which could prove advantageous for deprotection at a later stage.[3] The stability towards strong bases such as alkyllithium reagents was not expected to be high. The phosphate monoanion is prone to act as a leaving group in an E2-process, which is more likely for a tertiary than secondary center. Di-*t*-butyl hexyl and di-*t*-butyl isobutyl phosphate (**8a,b**) were prepared easily in 75 and 74% yield as given in Scheme 2, using freshly prepared di-*t*-butyl bromophosphate[4] and then subjected[1] to the phosphate-phosphonate rearrangement at −78 °C. Phosphate **8a** gave α-hydroxyhexylphosphonate (±)-**10a** in 65% yield in diethyl ether at a reaction time of 16 h and 76% yield in *n*-hexane at a reaction time of 26 h. These results demonstrate that the *t*-butyl groups are slowing down the reaction rate compared to the isopropyl groups (compare Table I) and elimination does not seem to be significant. Phosphate **8b** afforded the corresponding α-hydroxyphosphonate (±)-**10b** in 45% yield in hexane (26 h). As no starting material was present in the crude product, the low yield was attributed to the formation of isobutene and the water soluble lithium salt of *t*-butyl isobutyl phosphate. Deprotonation of **9b** is hindered by the two bulky *t*-butyl groups and the isopropyl group, thus making elimination more likely.



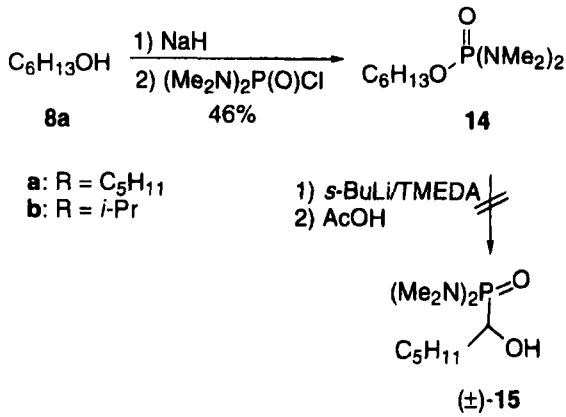
SCHEME 2 Synthesis and isomerisation of di-*t*-butyl phosphates **8a,b**

A neopentyl group is very resistant towards deprotonation for steric reasons. It was therefore worth trying to replace the two isopropyl groups in phosphate **1** by a 2,2-dimethylpropane-1,3-diyl group knowing that it is very resistant towards hydrolysis.[15] Phosphate **12** was prepared easily from cyclic phosphite **11**[16] and subjected to the phosphate-phosphonate rearrangement under the standard conditions to get the desired α-hydroxyphosphonate (±)-**13** (Scheme 3). As the crude product was an intractable mixture of several compounds as evidenced by ^{31}P and ^{1}H NMR spectroscopy, the use of the 2,2-dimethylpropane-1,3-diyl group as protecting group was abondoned.

At last, the dimethylamino group was tested as protecting group. The corresponding phosphoramidate **14**[17] was treated with *s*-BuLi/TMEDA in diethyl ether for 24 h at −78 °C, but no reaction occured (TLC) (Scheme 4). Therefore, the mixture was kept for another 5 h at -35 °C. Interestingly, only an impure trace (3%) of α-hydroxyphosphonamidate (±)-**15** could be isolated from the crude product. The two dimethylamino groups at phosphorus decrease the acidity of the hydrogens of the CH_2O group to an extent, that metallation does not work any more. Dialkylamino groups are not compatible with the phosphate-phosphonate rearrangement of aliphatic alcohols.



SCHEME 3 Preparation and rearrangement of cyclic phosphate **12**

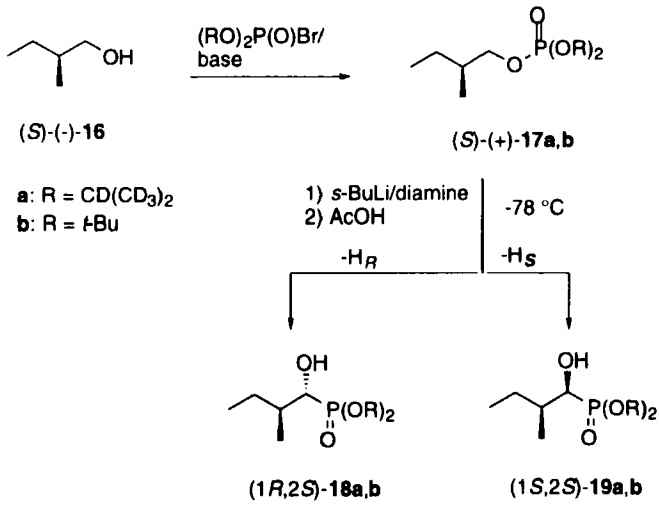


SCHEME 4 Synthesis and rearrangement of phosphoramidate **14**

Metallation of Phosphates Derived from (S)-2-Methylbutanol and Enantioselective Synthesis of α-Hydroxyphosphonates

To study the influence of a neighbouring chiral center carrying only alkyl groups on the metallation, we selected the di(heptadeuterioisopropyl) and di-*t*-butyl phosphate of (*S*)-2-methylbutanol [(*S*)-(-)-**16**] as substrates (Scheme 5). The α-hydroxyphosphonates **18** are starting materials for the

synthesis of the phosphonic acid analogs of isoleucine.[5] As the intermediate α-phosphonyloxy-substituted carbanions are configurationally stable and rearrange with retention of configuration, the ratio of the diastereomeric α-hydroxyphosphonates formed is determined by the metallation.[1] The di(heptadeuterioisopropyl) phosphate (*S*)-(-)-**17a** was isomerised in diethyl ether using *s*-BuLi with TMEDA and (-)-sparteine as diamines. After reaction times of 18 and 22 h, inseparable mixtures of the diastereomeric α-hydroxyphosphonates (1*R*,2*S*)-**18a** and (1*S*,2*S*)-**19a** were obtained in 72% (de 5%, by ^{1}H NMR) and 67% (de 7%) yield, respectively. The resonances of 1-H [d = 3.69 (dd, *J* = 3.9, 8.4 Hz), d = 3.52 (t, *J* = 6.3 Hz)] of the diastereomers are well separated in the ^{1}H NMR spectra. On the basis of literature data,[5] the signal at lower field was assigned to (1*S*,2*S*)-**19a** which was the major diastereomer in both cases. It shows, that the pro-*S* hydrogen of the CH_2O group of phosphate **17a** is easier removed than the pro-*R* hydrogen on metallation. The di-*t*-butyl phosphate (*S*)-(-)-**17b** was transformed similarly into a mixture of α-hydroxyphosphonates (1*R*,2*S*)-**18b** and (1*S*,2*S*)-**19b** in 40% yield (de 14%). The discriminating steric influence of a methyl and an ethyl group on the metallation is too small to be of importance. The presence of an alkoxy or dialkylamino group at C-2 of the primary alcohol will undoubtedly have much more directing effect.

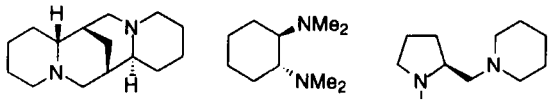


SCHEME 5 Synthesis and rearrangement of phosphates (*S*)-(-)-**17a,b**

Chiral, nonracemic α-hydroxyphosphonates are versatile starting materials for the synthesis of other α-substituted phosphonates and phosphonic acids. The enantioselective version of the phosphate-phosphonate rearrangement represents a new method for their preparation. Benzylic phosphates have been deprotonated by homochiral lithium amides and *s*-BuLi/(-)-sparteine to give optically active α-hydroxyphenylmethylphosphonates with enantiomeric excesses of up to 52 and 9%, respectively.[8] As alkyl phosphates are not metallated by lithium amides, we decided to use *s*-BuLi as base in combination with a homochiral diamines such as **20**[9] [(-)-sparteine], (1*R*,2*R*)-**21**[10] or (*S*)-**22**[11] (Figure 1). In the first place, di-*t*-butyl hexyl phosphate served as substrate at −78 °C in THF, diethyl ether, and hexane (Table II). The enantiomeric excesses were determined using 2 equivalents of (*S*)-(-)-*t*-butyl(phenyl)monothiophosphinic acid as chiral solvating agent.[12] The ^{1}H and ^{31}P NMR spectra were recorded in deuterated benzene. The results are compiled in Table II. The preferentially formed α-hydroxyphosphonate (+)-**10a** has (*S*) configuration based on ^{31}P NMR spectroscopy with the chiral solvating agent and the finding that (+)-diisopropyl 1-hydroxyhexylphosphonate has (*S*) configuration.[13] The reaction rates with *s*-BuLi/(-)-sparteine are significantly reduced compared to *s*-BuLi/TMEDA (with which the rearrangement was virtually finished after 3 h in diethyl ether, hexane, and THF). Some starting material was usually present in the crude products. The enantioselectivity was very low in THF (Entry 1, ee 5%) and medium in diethyl ether and hexane (Entries 2, 3 and 4, ee 40% versus 48%) at yields of 36 and 40%, respectively. By going from −78 to −35 °C the reaction rate increased at the expense of the ee (Entry 5, ee 9%, 6% of starting material was recovered). The C_2-symmetric N,N,N′,N′-tetramethyl-1,2-diaminocyclohexane [(1*R*,2*R*)-**21**] gave the smallest enantiomeric excesses (3 – 7%) and the highest yields (42 – 87%) of the three diamines, being caused by increased reaction rates relative to (-)-sparteine (Entries 6 to 8). The enantiomeric excesses (ee 13 – 17%) of the α-hydroxyphopshonate (+)-**10a** obtained with commercially available (*S*)-proline derived diamine (*S*)-**22** were higher than with (1*R*,2*R*)-**21**, but lower than with (-)-sparteine (Entries 9 to 11). The yields were very low (14 – 21%).

For comparison, two more phosphates were rearranged to the corresponding α-hydroxyphosphonates. Bis(heptadeuterioisopropyl) hexyl phosphate was metallated with *s*-BuLi/(-)-sparteine in diethyl ether at −78 °C for 22 h. The α-hydroxyhexylphosphonate was isolated in 67% yield,

which was virtually racemic [ee 3%; (*S*)]. When *n*-BuLi/(-)-sparteine was tested to induce the phosphate-phosphonate rearrangement of hexyl diisopropyl phosphate (diethyl ether, −78 °C, 18 h), 67% of the starting material was recovered and only a trace of racemic α-hydroxyphosphonate was isolated.



(-)-sparteine (**20**) (1*R*,2*R*)-**21** (*S*)-**22**

FIGURE 1 Structures of diamines

TABLE II Enantioselective rearrangement of di-*t*-butyl hexyl phosphate (**9a**) at −78 °C

Entry	*Diamine*	*Solvent*	*Time (h)*	$[\alpha]_D^{20}$ (*c*)[a]	*ee (%)*[b]	*Yield (%)*
1	**20**	THF	45	+0.46 (2.0)	5	42
2	**20**	Et_2O	43	+5.27 (2.0)	40 (44)	36
3	**20**	*n*-hexane	20	+5.29 (2.3)	36 (34)	25
4	**20**	*n*-hexane	43	+6.06 (2.0)	48	40
5[c]	**20**	*n*-hexane	6.5	+0.61 (1.8)	9	52
6	**21**[d]	THF	20	+1.15 (2.0)	3 (4)	42
7	**21**[d]	Et_2O	20	+0.57 (2.1)	7 (6)	73
8	**21**[d]	*n*-hexane	45	+0.66 (2.0)	7 (6)	87
9	(*S*)-**22**	Et_2O	26	+1.21 (2.0)	14 (13)	17
10	(*S*)-**22**	Et_2O	45	+1.66 (2.0)	13 (15)	21
11	(*S*)-**22**	*n*-hexane	45	+1.77 (1.8)	17 (14)	14

a. In acetone; c was rounded to the the nearest tenth.
b. Ee as determined by ^1H NMR spectroscopy (^{31}P) using (*S*)-(-)-*t*-butyl-phenylmonothiophosphinic acid as CSA and C_6D_6 as solvent.
c. This reaction was carried out at −35 °C.
d. (1*R*,2*R*)-**21**.

Di-*t*-butyl isobutyl phosphate **9b** gave phosphonate (*S*)-**10b** in diethyl ether at −78 °C after 48 h in only 13% yield with an ee of 62%. The methyl group at C-2 of the alcohol shielded the CH_2O additionally, causing the drop in reaction rate and the increased enantioselectivity compared to di-*t*-butyl hexyl phosphate. The consistant formation of (*S*) configurated α-hydroxyphosphonates with (-)-sparteine implies that the pro-*S* hydro-

gens at C-1 of the primary alcohols are removed preferentially, although with low selectivity. Hoppe et al found that carbamates of primary alcohols are also metallated by *s*-BuLi/(-)-sparteine with removal of the pro-*S* hydrogens.[9]

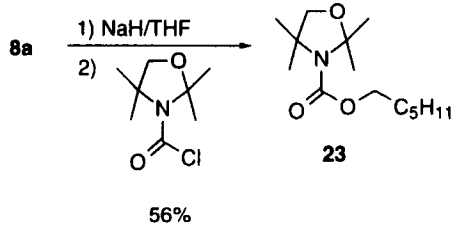
Experimental Estimation of Relative Acidity of α-Hydrogens of Hexanol Transformed into a Phosphate and a Carbamate

To determine the relative acidity of hydrogens α to oxygen in a phosphate and a carbamate, we set up an experiment to evaluate the activating influence of the two groups. A mixture of 1 mmol of each di-*t*-butyl hexyl phosphate (**9a**) and hexyl 2,2,4,4-tetramethyl-1,3-oxazolidine-3-carboxylate (**23**) prepared by a literature[14] procedure, were treated with 2 mmol of *s*-BuLi/TMEDA in diethyl ether at −78 °C (Scheme 6). After 3 h, the reaction was quenched with AcOD and worked up. A ^{31}P NMR spectrum was recorded from the crude product to determine the ratio of α-hydroxyphosphonate (-)-**10a** and phosphate **9a** (47:53). Flash chromatography furnished the carbamate, which was deuterated negligibly, if at all (6%, by ^{1}H NMR). When the carbamate was treated alone with *s*-BuLi/TMEDA under similar conditions, the deuterium contents of recovered carbamate **23** was 7%. This result prooves that the phosphate does not interfere with the metallation of the carbamate. Assuming that the hydrogens of the CH_2O group in both compounds are equally well accessible, the hydrogens of the phosphate are more activated (more acidic) than that of the carbamate.

CONCLUSIONS

We have found that the regioselectivity of metallation of diisopropyl hexyl phosphate is influenced by the solvent, the temperature, and the base. At −94 °C, deprotonation occurs exclusively at the methylene group. The corresponding di-*t*-butyl phosphate is metallated regioselectively by *s*-BuLi/TMEDA. The dimethylamino group as protecting group blocks deprotonation. When TMEDA was replaced by homochiral diamines, enantioenriched α-hydroxyphosphonates were obtained. Although the ee was at best 48%, an enantioselective version of the phosphate-phosphonate rearrangement is feasable. The dialkoxyphosphonyl group is a

stronger activating group for metallation of primary alcohols than the carbamoyl group.



SCHEME 6 Preparation of carbamate **23**

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$, unless otherwise given, using tetramethylsilane as internal standard on a Bruker AM 400 WB at 400.13 and 100.61 MHz, respectively. ^{31}P NMR spectra were recorded on the same spectrometer at 161.97 MHz using H_3PO_4 (85%) as external standard. In order to get 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 run on a Perkin Elmer 1600 FT-IR spectrometer as films between NaCl plates or on a silicon plate.[15] Optical rotations were measured at 20 °C on a Perkin Elmer 241 polarimeter in a 1 dm cell. TLC was carried out on 0.25 mm thick Merck plates, silica gel 60 F_{254}. Flash chromatography was performed with Merck silica gel 60 (230 – 400 mesh). Spots were visualized by dipping into a solution of 24 g of $(NH_4)_6Mo_7O_{24}.4H_2O$ and 1 g of $Ce(SO_4)_2.4H_2O$ in 500 ml of 10% H_2SO_4 in water, followed by heating with a hot gun. (1*R*,2*R*)-N,N,N′,N′-Tetramethyl-1,2-diaminocyclohexane was prepared by Eschweiler Clarke reaction in 77% yield.[16]

General Procedure for the Preparation of Alkyl di-tert-butyl phosphates

To a stirred solution of potassium bis(trimethylsilyl)amide (4.02 g, 20.14 mmol, 1.3 equiv., 95%) in dry THF (40 ml) at −78 °C under argon a solu-

tion of alcohol (15.5 mmol) in dry THF (10 ml) was added dropwise. After 30 min, a solution of crude di-*tert*-butyl bromophosphate[14] (6.3 g, 23 mmol, 1.5 equiv., dried for 1 h at 20 °C/0.3 mm) in dry THF (5 ml) was added. The reaction mixture was allowed to warm up in the cooling bath from −78 °C to +15 °C over night. The bath was removed and stirring was continued at room temperature (for duration see individual compounds). Water (5 ml) was added and after 30 min the mixture was concentrated in vacuo. The residue was taken up in water (100 ml) and the product was extracted with CH_2Cl_2 (4 × 40 ml). The combined organic layers were washed with water, dried (Na_2SO_4) and concentrated in vacuo. The crude product was flash chromatographed.

Di-tert-butyl hexyl phosphate (9a)

1-Hexanol (1.58 g, 1.93 ml, 15.5 mmol) was phosphorylated according to the general procedure. The reaction mixture was stirred for 30 min at room temperature at the end. The crude product was purified by flash chromatography (hexanes/EtOAc 5:1, $R_f = 0.24$), followed by bulb to bulb distillation (bp. 75 °C/0.1 mm) to give phosphate **9a** as a colourless liquid (3.42 g, 75%). – IR (Si): $\nu_{max} = 2980$ cm^{-1}, 2985, 2933, 1370, 1267, 1040, 998. – ^{1}H NMR: $\delta = 0.82$ (t, $J = 7.0$ Hz, 3H, CH_3CH_2), 1.27 (m, 6H, CH_2), 1.41 (s, 18H, *t*-Bu), 1.58 (quin, $J = 6.9$ Hz, 2H, CH_2), 3.88 (q, $J = 6.9$ Hz, 2H, OCH_2). – ^{13}C NMR: $\delta = 13.96$ (CH_3CH_2), 22.52 (CH_2), 25.27 (CH_2), 29.85 [d, $J = 4.2$ Hz, $(CH_3)_3C$], 30.20 (d, $J = 7.5$ Hz, CH_2), 31.36 (CH_2), 66.88 (d, $J = 6.6$ Hz, CH_2O), 81.84 [d, $J = 7.1$ Hz, $(CH_3)_3C$]. – ^{31}P NMR: $\delta = -8.35$. – $C_{14}H_{31}O_4P$ (294.37); calcd. C 57.12, H 10.62; found C 57.55, H 10.67.

Di-tert-butyl isobutyl phosphate (9b)

Isobutanol (0.608 g, 0.76 ml, 8.2 mmol) was phosphorylated according to the general procedure. At the end, the reaction mixture was stirred at room temperature for 3.5 h. The crude product was purified by flash chromatography (hexanes/EtOAc 5:1, $R_f = 0.21$), followed by bulb to bulb distillation (bp. 65–70 °C/0.1 mm) to give phosphate **9b** as a colourless liquid (1.62 g, 74%). – IR (Si): $\nu_{max} = 2979$ cm^{-1}, 2937, 1474, 1395, 1370, 1269, 1176, 1039, 1000. – ^{1}H NMR: $\delta = 0.88$ [d, $J = 6.7$ Hz, 6H, $(CH_3)_2CH$], 1.41 (s, 18H, *t*-Bu), 1.88 [non, $J = 6.5$ Hz, 1H, $(CH_3)_2CH$], 3.65 (t, $J = 6.7$ Hz, 2H, OCH_2). – ^{13}C NMR: $\delta = 18.79$ [d, $J = 14.5$ Hz,

$(CH_3)_2CH]$, 28.95 (d, J = 7.8 Hz, CH), 29.85 [d, J = 4.2 Hz, $(CH_3)_3C]$, 72.90 (d, J = 6.8 Hz, OCH_2), 81.84 [d, J = 7.3 Hz, $(CH_3)_3C]$. – ^{31}P NMR: δ = –8.31.

(±)-Di-tert-butyl 1-hydroxyhexylphosphonate [(±)-10a]

Phosphate **9a** (0.294 g, 1 mmol) was rearranged[11] with *s*-BuLi/TMEDA (2 mmol of each) in diethyl ether or *n*-hexane as reported previously. The crude product was purified by flash chromatography (hexanes/EtAc 2:1, R_f= 0.19) to yield crystalline (±)-**10a** (0.190 g, 65% in diethyl ether; 0.225 g, 76% in *n*-hexane); mp. 54–56 °C (hexanes/diethyl ether). – IR (Si): ν_{max} = 3313 cm^{-1}, 2979, 2957, 1370, 1257, 1233, 1169, 1040, 987. – ^{1}H NMR: δ = 0.83 (t, J = 6.9 Hz, 3H, CH_3CH_2), 1.25 (m, 5H, CH_2), 1.44 (s, 9H, *t*-Bu), 1.53 (m, 2H, CH_2), 1.67 (m, 1H, CH_2), 2.25 (br.s, 1H, OH), 3.56 (dt, J= 9.4 Hz, 3.5 Hz, 1H, PCH). – ^{13}C NMR: δ = 14.01 (CH_3CH_2), 22.54 (CH_2), 25.65 (d, J = 12.4 Hz, CH_2), 30.52 [d, J = 3.7 Hz, $(CH_3)_3C]$, 31.57 (CH_2), 31.78 (CH_2), 69.62 (d, J = 164.0 Hz, CHP), 82.51 [d, J = 9.4 Hz, $(CH_3)_3C]$, 88.57 [d, J = 9.8 Hz, $(CH_3)_3C]$. – ^{31}P NMR: δ = 18.71. – $C_{14}H_{31}O_4P$ (294.37): calcd. C 57.12, H 10.62; found C 57.30, H 10.37.

(±)-Di-tert-butyl 1-hydroxy-2-methylpropylphosphonate [(±)-10b]

Phosphate **9b** (0.266 g, 1 mmol) was rearranged with *s*-BuLi/TMEDA (2 mmol of each) in *n*-hexane as reported previously (reaction time: 26 h). The crude product was purified by flash chromatography (hexanes/EtOAc 2:1, R_f= 0.14) to yield α-hydroxyphosphonate (±)-**10b** (0.119 g, 45%) as a colourless oil. – IR (Si): ν_{max} = 3323 cm^{-1}, 2981, 1366, 1258, 1203, 1168, 1042, 997. – ^{1}H NMR: δ = 0.97 (d, J = 6.5 Hz, 3H, $(CH_3)_2CH]$, 0.98 (d, J = 6.5 Hz, 3H, $(CH_3)_2CH)$, 1.44 (s, 9H, *t*-Bu), 1.45 (s, 9H, *t*-Bu), 1.96 [dsept, J = 15.6, 6.5 Hz, 1H, $(CH_3)_2CH]$, 2.25 (br.s, 1H, OH), 3.32 (dd, J = 6.5, 5.0 Hz, 1H, CHP). – ^{13}C NMR: δ = 18.19 [d, J = 8.8 Hz, $(CH_3)_2CH]$, 20.03 [d, J = 8.0 Hz, $(CH_3)_2CH]$, 30.90 [$(CH_3)_2CH]$, 30.92 [d, J = 3.8 Hz, $(CH_3)_3C]$, 30.96 [d, J = 3.8 Hz, $(CH_3)_3C]$, 75.31 (d, J = 158.3 Hz, CHP), 83.04 [d, J = 10.0 Hz, $(CH_3)_3C]$, 83.21 [d, J = 10.0 Hz, $(CH_3)_3C]$. – ^{31}P NMR: δ = 18.87.

2-Hexyloxy-5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinane (12)

A stirred solution of 2-H-5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinane (**11**)[6] (3.60 g, 24 mmol) and dry pyridine (3.8 g, 3.9 ml, 48 mmol) in dry

CH_2Cl_2 (25 ml) was cooled to 0 °C under argon. Tetrabromomethane (7.96 g, 25 mmol) was added, followed by a solution of 1-hexanol (3.0 g, 3.7 ml, 20 mmol) in dry CH_2Cl_2 (25 ml) within 30 min. The reaction mixture was stirred for 21 h at room temperature, washed with HCl (2 M), water and a saturated aqueous solution of $NaHCO_3$, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash chromatography (hexanes/EtOAc 2:1, R_f= 0.23) followed by bulb to bulb distillation (bp. 115–118 °C/0.04 mm) to yield cyclic phosphate **12** as a colourless liquid (3.67 g, 73%). – IR (Si): ν_{max} = 2959 cm^{-1}, 2933 1473, 1299, 1072, 1055, 1008. – ^1H NMR: δ = 0.87 (t and s overlapping, 6H, CH_3), 1.21 (s, 3H, CH_3), 1.31 (m, 6H, CH_2), 1.67 (quin, J = 6.9 Hz, 2H, CH_2), 3.88 (m, 2H, CCH_2O), 4.04 (m, 4H, CCH_2O and CH_2CH_2O). – ^{13}C NMR: δ = 13.60 (CH_3CH_2), 20.14 [$(CH_3)_3C$], 21.27 [$(CH_3)_3C$], 22.14 (CH_2), 24.78 (CH_2), 29.88 (d, J = 6.4 Hz, CH_2), 30.99 (CH_2), 31.80 [d, J = 5.7 Hz, $(CH_3)_3C$], 67.31 (d, J = 5.8 Hz, OCH_2CH_2), 77.31 (d, J = 6.6 Hz, 2C, CCH_2O). – $C_{11}H_{23}O_4P$ (250.28): calcd. C 52.79, H 9.26; found C 52.62, H 9.03.

N,N,N',N'-Tetramethyl hexyl phosphordiamidate (14)[7]

To a stirred mixture of NaH (0.440 g of a dispersion in mineral oil, 55–65%, washed twice with 15 ml of hexanes, 10 mmol of NaH) in dry THF (2.5 ml) was added under argon a solution of 1-hexanol (1.124 g, 1.37 ml, 11 mmol) in dry THF (3.5 ml). After refluxing for 1.5 h, it was cooled to –20 °C and the $(Me_2N)_2P(O)Cl$ (1.90 g, 1.65 ml, 10 mmol; 90%, technical grade) was added dropwise. The mixture was allowed to warm up gradually in the bath to –8 °C, it was then stirred for 30 min at room temperature and was finally quenched with water (5 ml). Extraction with CH_2Cl_2 (4 × 15 ml) gave organic layers which were combined, washed with water (10 ml), dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by flash chromatography (EtOAc; TLC: hexanes/EtOAc 1:2, R_f= 0.10), followed by bulb to bulb distillation (bp. 140–142 °C/10 mm) (lit.[7] 131 °C/4–5 mm) to give **14** as a colourless liquid (1.09 g, 46%). – IR (Si): ν_{max} = 2930 cm^{-1}, 2858, 1459, 1303, 1223, 1061, 1044, 990. – ^1H NMR: δ = 0.82 (t, J = 6.8 Hz, 3H, CH_3CH_2), 1.26 (m, 6H, CH_2), 1.57 (quin, J = 6.8 Hz, 2H, CH_2), 2.58 (d, J = 9.8 Hz, 12H, Me_2N), 3.83 (q, J = 6.8 Hz, OCH_2),

(S)-(+)-Bis(heptadeuterioisopropyl) 2-methylbutyl phosphate [(S)-(+)-17a]

(*S*)-(-)-2-Methylbutanol (0.529 g, 0.65 ml, 6 mmol, ee 98%) was phosphorylated with bis(heptadeuterioisopropyl) bromophosphate/pyridine.[11] Purification of the crude product by flash chromatography (hexanes/EtOAc 3:1, R_f= 0.27) and bulb to bulb distillation (bp. 60–65 °C/0.01 mm) furnished phosphate (*S*)-(+)-**17a** as a colourless liquid (1.293 g, 74%); $[\alpha]_D^{20}$ = +1.41 (*c* 1.99, acetone). – IR (Si): ν_{max} = 2964 cm^{-1}, 2233 (C-D), 1285, 1271, 1237, 1159, 994. – ^1H NMR: δ = 0.80 (t, *J* = 7.4 Hz, 3H, CH_3CH_2), 0.83 (d, *J* = 6.4 Hz, 3H, CH_3CH), 1.08 (m, 1H, CH_3CH_2), 1.36 (m, 1H, CH_3CH_2), 1.60 (oct, *J*= ~6.4 Hz, 1H, CH), 3.68 (A part of ABXY system, J_{AB} = 9.4 Hz, *J* = 6.4, 5.9 Hz, 1H, OCH_2), 3.75 (B part of ABXY system, J_{AB} = 9.4 Hz, $J_1 = J_2$ = 5.9 Hz, 1H, OCH_2). – ^{13}C NMR: δ = 11.10 (CH_3), 16.00 (CH_3), 25.51 (CH_2), 35.40 (d, *J* = 7.6 Hz, CH), 71.72 (d, *J* = 6.3 Hz, OCH_2). – ^{31}P NMR: δ = –1.67. – $C_{11}H_{11}D_{14}O_4P$ (266.18): calcd. C 49.64, H 4.17, D 10.50, P 11.64; found (H and D were detected with the same sensitivity) C 49.35, H+D 9.55, P 11.90.

(S)-(+)-Di-tert-butyl 2-methylbutyl phosphate [(S)-(+)-17b]

(*S*)-(-)-2-Methylbutanol (0.441 g, 0.54 ml, 5 mmol, ee 98%) was phosphorylated according to the general procedure. At the end, the reaction mixture was stirred at room temperature for 1.5 h. The crude product was purified by flash chromatography (hexanes/EtOAc 5:1, R_f= 0.22), followed by bulb to bulb distillation (bp. 57–63 °C/0.2 mm) to give phosphate (*S*)-(+)-**17b** as a colourless liquid (0.982 g, 70%); $[\alpha]_D^{20}$ = +0.91 (*c* 2.19, acetone), $[\alpha]_{365}^{20}$ = +3.11. – IR (Si): ν_{max} = 2979 cm^{-1}, 2936, 1465, 1395, 1371, 1265, 1175, 1040, 1000. – ^1H NMR: δ = 0.88 (t, *J* = 7.5 Hz, 3H, CH_3CH_2), 0.91 (d, *J* = 7.0 Hz, 3H, CH_3CH), 1.15 (m, 1H, CH_3CH_2), 1.44 (m, 1H, CH_3CH_2), 1.45 (s, 18H, *t*-Bu), 1.67 (oct, *J* = ~7.0 Hz, 1H, CH), 3.71 (A part of ABXY system, J_{AB} = 9.5 Hz, $J_1 = J_2$ = 6.0 Hz, 1H, OCH_2), 3.78 (B part of ABXY system, J_{AB} = 9.5 Hz, $J_1 = J_2$ = 5.8 Hz, 1H, OCH_2). – ^{13}C NMR: δ = 11.14 (CH_3), 16.12 (CH_3), 25.60 (CH_2), 29.86 [d, *J* = 3.8 Hz, $(CH_3)_3C$], 35.36 (d, *J* = 7.7 Hz, CH), 71.28 (d, *J* = 6.9 Hz, OCH_2), 81.80 [d, *J* = 7.7 Hz, $(CH_3)_3C$]. – ^{31}P NMR: δ = –8.20. – $C_{13}H_{29}O_4P$ (280.35): calcd. C 55.70, H 10.43; found C 55.89, H 9.93.

(1R,2S)- and (1S,2S)-Bis(heptadeuterioisopropyl) 1-hydroxy-2-methylbutylphosphonate [(1R,2S)- and (1S,2S)-19a]

Phosphate (*S*)-(+)-**17a** (0.266 g, 1 mmol) was rearranged with *s*-BuLi/TMEDA or *s*-BuLi/(-)-sparteine (2 mmol of each) in diethyl ether as reported previously [reaction time: 18 h with TMEDA, 22 h with (-)-sparteine].[11] The crude products were purified by flash chromatography (hexanes/EtOAc 1:1, $R_f = 0.26$) to yield mixtures of α-hydroxyphosphonates (1*R*,2*S*)- and (1*S*,2*S*)-**19a** [TMEDA: 0.202 g, 45%, de 5% (^{1}H NMR); (-)-sparteine: 0.188 g, 67%, de 7%] as colourless oils. – IR (Si): $\nu_{max} = 3313\ cm^{-1}$, 2965, 2231 (C-D), 1235, 1157, 1073, 1046, 1012, 982. – ^{1}H NMR: δ = 0.88 (minor) and 0.89 (major) (2t, *J* = 7.4 Hz, 3H, CH_3CH_2), 1.00 (minor) and 1.01 (major) (2d, *J* = 6.9 Hz, 3H, CH_3CH), 1.27 (m, 2H), 1.53 (sept, *J* = 7.4 Hz, 1H, CH_3CH), 1.78 (m, 3H), 2.35 (br.s, 1H, OH), 3.56 (t, *J* = 6.4 Hz, CHP, minor) and 3.72 (dd, *J* = 8.4, 3.9 Hz, CHP, major) (1H). – ^{31}P NMR: δ = 24.46 (major), 24.72 (minor).

(1R,2S)- and (1S,2S)-Di-tert-butyl 1-hydroxy-2-methylbutylphosphonate [(1R,2S)- and (1S,2S)-19b]

Phosphate (*S*)-(+)-**17b** (0.280 g, 1 mmol) was rearranged with *s*-BuLi/TMEDA in diethyl ether as reported previously (reaction time: 24 h).[11] The crude product was purified by flash chromatography (hexanes/EtOAc 2:1, $R_f = 0.19$) to yield a crystalline mixture of α-hydroxyphosphonates (1*R*,2*S*)- and (1*S*,2*S*)-**19a** [0.099 g, 40%, de 13% (^{1}H NMR)]. – IR (Si): $\nu_{max} = 3324\ cm^{-1}$, 2976, 1369, 1257, 1210, 1167, 1043, 989; ratio major/minor 1:0.763, de 14% (by ^{1}H NMR). – ^{1}H NMR: δ = 0.88 (minor) and 0.89 (major) (2t, *J* = 7.4 Hz, 3H, CH_3CH_2), 0.99 (minor) and 1.00 (major) (2d, *J* = 6.5 Hz, 3H, CH_3CH), 1.26, 1.53 and 1.77 (3m, 3H, CH_3CH_2, CH_3CH), 1.487, 1.490 and 1.495 (3 partly overlapping s of different intensity, 18H, *t*-Bu), 2.24 (t, *J* = 7.0 Hz, OH, major) and 2.39 (dd, *J* = 7.5, 5.0 Hz, OH, minor) (1H), 3.42 (dt, *J* = 7.0, 5.0 Hz, CHP, minor) and 3.57 (dt, *J* = 7.0, 4.0 Hz, CHP, major) (1H). – ^{13}C NMR: δ = 10.96 (CH_3CH_2, minor), 11.64 (CH_3CH_2, major), 14.11 (d, *J* = 5.4 Hz, CH_3CH, major), 15.73 (d, *J* = 6.1 Hz, CH_3CH, minor), 24.71 (d, *J* = 9.2 Hz, CH_3CH_2, minor), 26.77 (d, *J* = 10.7 Hz, CH_3CH_2, major), 30.51 [d, *J* = 3.8 Hz, $(CH_3)_3C$], 30.55 [d, *J* = 4.6 Hz, $(CH_3)_3C$], 36.66 (PCCH, major), 37.06 (PCCH, minor), 72.67 (d, *J* = 159.9 Hz, PCH, major), 73.98 (d, *J* = 159.1 Hz, PCH, minor), 82.62 (d, *J* = 9.9 Hz, $(CH_3)_3C$], 82.65 (d,

J = 9.9 Hz, $(CH_3)_3C$], 82.74 (d, J = 9.9 Hz, $(CH_3)_3C$], 82.78 (d, J = 9.9 Hz, $(CH_3)_3C$]. – ^{31}P NMR: δ = 19.05 (major), 19.38 (minor). – $C_{13}H_{29}O_4P$ (280.35): calcd. C 55.70, H 10.43; found C 55.98, H 10.26.

Hexyl 2,2,4,4-tetramethyl-1,3-oxazolidine-3-carboxylate (23)

A solution of 1-hexanol (1.4 ml, 11 mmol) in dry THF (10 ml) was added to a stirred mixture of NaH (0.65 g of a dispersion in mineral oil, 55%, washed twice with 15 ml of hexanes, 14.9 mmol of NaH) in dry THF (20 ml) under argon. After refluxing for 30 min, a solution of 2,2,4,4-tetramethyl-1,3-oxazolidine-3-carbonyl chloride (1.96 g, 10 mmol; prepared according to the literature procedure[14] except that it was not refluxed, but stirred at room temperature[17] for 16 h) in dry THF (7 ml) was added and refluxing was continued for another 5 h. The reaction mixture was cooled, diluted with diethyl ether (50 ml) and washed with HCl (0.25 M, 30 ml). The aqueous phase was separated and extracted with diethyl ether (2 × 20 ml). The combined three organic layers were washed with a saturated aqueous solution of $NaHCO_3$, dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (hexanes/diethyl ether 8:1, R_f = 0.40) of the residue and bulb to bulb distillation (bp. 125 °C/18 mm) gave carbamate **23** as a colourless liquid (1.44 g, 56%). – IR (NaCl, film): ν_{max} = 2932 cm^{-1}, 2862, 1702, 1407, 1343, 1260, 1097, 1071; ratio of conformers 60:40 (NMR). – ^{1}H NMR: δ = 0.90 (2 overlapping t, J = 6.9 Hz, 3H, CH_2CH_3), 1.28–1.40 (m, 6H, CH_2), 1.37 and 1.56 (2s, $NC(CH_3)_2CH_2$ and $NC(CH_3)_2O$, major), 1.43 and 1.52 [2s, $NC(CH_3)_2CH_2$ and $NC(CH_3)_2O$, minor], 1.65 (m, 2H, OCH_2CH_2), 3.72 (s, 2H, $NC(CH_3)_2CH_2$), 4.08 (2 overlapping br.t, J = 6.3 Hz, 2H, CH_2O). – ^{13}C NMR: δ = 13.91 (CH_3CH_2), 22.47 (CH_2), 24.12, 25.24, 25.27 and 26.46 [$C(CH_3)_2$], 25.77 (CH_2), 28.85 (CH_2), 31.37 (CH_2), 59.13 [$NC(CH_3)_2CH_2$, major], 60.00 [$NC(CH_3)_2CH_2$, minor], 76.07 [$NC(CH_3)_2CH_2$, minor], 76.32 [$NC(CH_3)_2CH_2$, major], 94.31 [$NC(CH_3)_2O$, minor], 95.27 [$NC(CH_3)_2O$, major], 151.79 (CO, minor), 152.50 (CO, major). – $C_{14}H_{27}NO_3$ (257.37): calcd. C 65.33, H 10.57; found C 65.45, H 10.68.

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