Tetrahedron: *Asymmetry* 22 (2011) 752–760

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Derivatizing agents from phosphorus trichloride and terpenyl tartrates for determining the enantiomeric purity of alcohols

Matthias Amberg, Irina Kempter, Uwe Bergsträßer, Georg Stapf, Jens Hartung *

Fachbereich Chemie, Organische Chemie, Technische Universität Kaiserslautern, Erwin-Schrödinger-Straße, D-67663 Kaiserslautern, Germany

ARTICLE INFO

Article history:
Received 14 March 2011
Accepted 4 April 2011

ABSTRACT

Heterocyclic phosphorous acid chlorides, prepared from C_2-symmetric menthyl, borneyl, or fenchyl tartrates and phosphorus trichloride, are inexpensive derivatizing agents for determining the enantiomeric purity of alcohols via phosphorus NMR. The most versatile agent identified from this study, a (1*R*,2*S*,5*R*)-menthyl (*R*,*R*)-tartrate-derived 2-chloro-1,3,2-dioxaphospholane, gives, upon esterification with chiral alcohols, diastereomeric phosphites showing phosphorus NMR-shift dispersions between 0.1 ppm and 1.5 ppm.

1. Introduction

Procedures for analyzing the enantiomeric purity of alcohols are important for development of synthetic methods dealing with oxidative transformations of unsaturated hydrocarbons,[1–3] enzyme-catalyzed desymmetrization of esters, or nucleophilic addition to carbonyl compounds.[4] To determine the enantiomeric purity of alcohols, three common approaches exist. The first approach is based on reversible adduct formation between an enantiomerically pure probe and enantiomers of a chiral alcohol. Differences in the type (connectivity) and degree (bond strength) of diasteromorphic interactions that result from molecular recognition may be enough to bring about changes in chromophores (UV/vis, IR) or shielding parameters of nuclei (NMR), to spectroscopically distinguish the diastereomorphs.[5–8] The second approach takes advantage of the differences in binding energies between a chiral analyte, which is the alcohol as the guest, and a large number of chiral receptors as hosts, mounted on a stationary phase along a flow gradient. By using this approach, retention time dispersion for the chromatographic separation of enantiomers is attainable (GC or HPLC).[9,10] In the third approach, enantiomers are modified via covalent bonding to an enantiomerically pure derivatizing agent, thus providing diastereomers for stereochemical characterization in an isotropic environment.[11,12]

A common strategy for determining the enantiomeric purity of alcohols via the derivitization approach uses (*R*)- or (*S*)-α-methoxy-α-trifluoromethylphenyl acetic acid (Mosher's acid) to esterify the analyte.[13] The acid, however, is expensive. With the need to reduce cost for analytical purposes without losing the generality of enantiomer analysis, chemists have invested effort to find phosphorus-based alternatives to Mosher's acid.[14–17] The phosphorus nucleus shows strong responsivity in shielding arising from steric, stereoelectronic, and electronic changes.[18,19] To simplify the stereochemical aspects dealing with synthesis and alcohol derivatizing, it is often advantageous to use phosphorus(III)-derived agents (phosphorus in a chirotopic environment) rather than phosphorus(V) compounds (stereogenic phosphorus). Phosphorus(III) compounds, however, hydrolyze rapidly and are sometimes demanding to prepare.[15,16]

To determine the enantiomeric purity of alcohols prepared from transition metal-catalyzed oxidation,[20] we needed an inexpensive chiral derivatizing agent with none of the familiar disadvantages (vide supra).[21,22] For economic reasons, we decided to use building blocks from the chiral pool, to prepare phosphorus(III) compounds that are largely inert toward hydrolysis (Fig. 1). The most important result herein shows that an agent synthesized from tartaric acid, menthol, and phosphorus trichloride fulfills the prerequisites. This compound is able to copy the enantiomeric ratios of alcohols (primary, secondary, and tertiary), via an in situ phosphite formation, into diastereomers and shows in the majority of cases, adequate shift dispersions to quantify results via the integration of baseline-separated phosphorus resonances.

2. Results and discussion

2.1. Preparation and properties of 2-chloro-1,3,2-dioxaphospholanes

The condensation of phosphorus trichloride and C_2-symmetric menthyl, borneyl, or fenchyl tartrates **2a**–**d**[23] in solutions of boiling dry tetrahydrofuran, gave 2-chloro-1,3,2-dioxaphospholanes **1a**–**d** in yields of between 72% and 88% (Table 1). To drive the condensation to completion, we added phosphorus trichloride in excess. The

* Corresponding author. Tel.: +49 631 205 2431; fax: +49 631 205 3921.
E-mail address: hartung@chemie.uni-kl.de (J. Hartung).

0957-4166/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2011.04.004

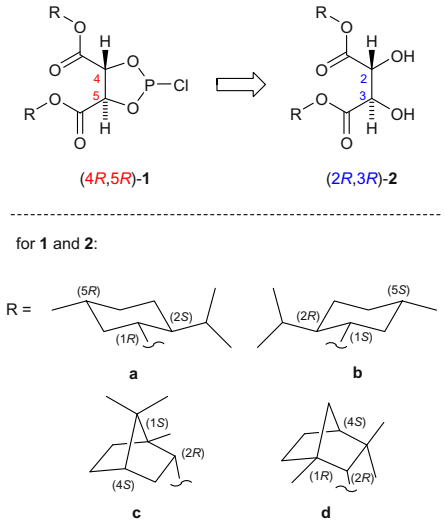
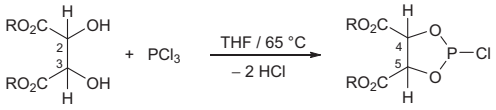


Figure 1. Structure formulae and indexing of chiral 2-chloro-1,3,2-dioxaphospholanes **1a**–**d** and tartrate-derived building blocks **2a**–**d**.

Table 1
Synthesis of tartrate-derived 2-chloro-1,3,2-dioxaphospholanes **1a**–**d**[a]



2a–**d** **1a**–**d**

Entry	**2**	Yield (%)	$[\alpha]_D^{25}$[b]	Mp (°C)	$\delta^{31}P$[c] (ppm)
1	(2*R*,3*R*)-**2a**	(4*R*,5*R*)-**1a**: 87	−155.0	72	175.6
2	(2*S*,3*S*)-**2b**	(4*S*,5*S*)-**1b**: 88	+151.4	70–71	175.6
3	(2*R*,3*R*)-**2b**	(4*R*,5*R*)-**1b**: 78	−20.6	67–68	175.5
4	(2*S*,3*S*)-**2a**	(4*S*,5*S*)-**1a**: 72	+21.3	69–70	175.5
5	(2*R*,3*R*)-**2c**	(4*R*,5*R*)-**1c**: 81	−105.0	82	174.8
6	(2*R*,3*R*)-**2d**	(4*R*,5*R*)-**1d**: 84	−17.0	80	176.3

[a] For indexing of R refer to Figure 1.
[b] *c* 1.00 in THF.
[c] In C_6D_6 at 25 °C.

solvent and excess phosphorus reagent were distilled off, to leave 2-chloro-1,3,2-dioxaphospholanes **1a**–**d** as colorless oils, which crystallized from cold pentane.

In solutions of chloroform-d_1 or benzene-d_6, protons attached to the C4 and C5 of chlorodioxaphospholanes **1a**–**d** differed in the chemical shift ($\Delta\delta_H$ = 0.5–0.6 ppm, 25 °C) and multiplicity. One of the protons forms a doublet ($^3J_{H,H}$ = 6.7–7.1 Hz) and the second a double doublet. The additional coupling ($^3J_{P,H}$ = 8.6–9.1 Hz; Fig. 2) comes from proton-phosphorus interaction, as evident from the phosphorus-decoupled proton NMR-spectra.

In the solid state, heterocyclic cores of (1*R*,2*S*,5*R*)-menthyl-substituted dioxaphospholane (4*R*,5*R*)-**1a** and (1*S*,2*R*,4*S*)-borneyl

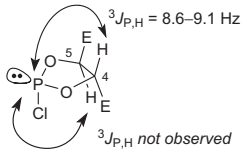


Figure 2. Visualization of the interactions between the phosphorus and diastereotopic protons at the 4- and 5-positions of 2-chloro-1,3,2-dioxaphosopholanes **1a**–**d** (E = ester substituent; for a model explaining the differences in the $^3J_{P,H}$-coupling with H4 and H5 on the basis of positioning of the pair of non-bonding electrons at phosphorus, see text).

derivative (4*R*,5*R*)-**1c** adopt twist (T) conformations, with the phosphorus atom and one of the endocyclic oxygens offset into opposite directions from a plane, which is formed by the C4 and C5 atoms and the second endocyclic oxygen [$^2T_3$-conformation[24] for (4*R*,5*R*)-**1a**, $_2T^3$-conformation for (4*R*,5*R*)-**1c**] (Fig. 3).

The non-equivalence of endocyclic phosphorus–oxygen bonds, with the shorter distance being situated in the least puckered region of the heterocycle, in combination with a lengthening of the phosphorus–chlorine bond (Table 2, entries 1–3), which is widened beyond the reference value given for phosphorus trichloride [2.043(3) Å],[25] is characteristic for solid state structures of saturated heterocycles composed of $ClPO_2$-subunits.[26–29] Similar parameters were reported for the structure of 2-chloro-1,3,2-dioxaphospholane in the gas phase.[30]

To rationalize the structural properties of the 2-chloro-1,3,2-dioxaphospholanes, we propose a model based on a stabilizing interaction between the p-type lone pair at the oxygen [p^2(O)] and the non-bonding orbital of the phosphorus–chlorine bond [$\sigma*$(P,Cl); Fig. 4], similar to the anomeric effect in carbohydrate chemistry.[31] This model explains the shortening of the phosphorus–oxygen bonds in the planarized part of the five-membered ring, the lengthening of the phosphorus–chlorine bond, and the conformational stability at the phosphorus atom. Furthermore the existence of a stereoelectronic effect explains breaking of the C_2-symmetry imposed by the dialkyl tartrate unit in heterocycles **1a**–**d** and thus the origin of an additional coupling caused by *syn*-orientation and thus through space interaction between the pair of non-bonding electrons at phosphorus and the proton attached to C4 (Fig. 2).[32–34]

2.2. Stability of 2-chloro-1,3,2-dioxaphospholanes

To clarify as to whether the new compounds would resist decomposition if stored under conditions that generally exist in our laboratory (~20 °C, ~50–80% relative humidity), we took samples from (4*R*,5*R*)-**1a** and (4*R*,5*R*)-**1b** over intervals and monitored the fraction of unspent 2-chloro-1,3,2-dioxaphospholane ($OPPh_3$ as an internal standard). After 24 h, samples stored in air consisted of ~95% of unchanged acid chlorides (4*R*,5*R*)-**1a** and (4*R*,5*R*)-**1b**. During this time, the outer appearance of the compounds remained the same. Samples of borneyl-substituted chlorodioxaphospholane (4*R*,5*R*)-**1c** and fenchyl derivative (4*R*,5*R*)-**1d** also showed no changes in outer appearance. We therefore, concluded that the stabilities of all 2-chlorodioxaphospholanes prepared in this study are quite similar.

The stability of **1** is an important improvement with respect to known derivatives, such as a compound prepared from diethyl tartrate and phosphorus trichloride,[16] which decomposes within less than 24 h, if stored in a laboratory atmosphere.[21] We believe that the considerable degree of inertness, is because of the crystallinity of acid chlorides **1a**–**d**, since the more labile congeners are oils.

2.3. Formation of trialkylphosphites

The analysis of enantiomeric purity via chemical derivatization requires quantitative esterification of a chiral alcohol (primary, secondary, and tertiary) with **1**. The enantiomeric ratio of the alcohol thereby is copied into a diastereomeric ratio of phosphites, which is analyzed via integration of the shift-dispersed phosphorus resonances.

To verify the in situ phosphite formation from (4*R*,5*R*)-**1a**, 1,1,1-trichloroethanol **5** was converted into trichloroethyl ester **6** in quantitative yield. In trichloroethyl ester **6**, the resonances of diastereotopic protons are split by a geminal proton–proton coupling (11.8 Hz) and a vicinal phosphorus-proton coupling (7.2–8.2 Hz) into double doublets (Table 3, entry 1; Fig. 5). The effect of the

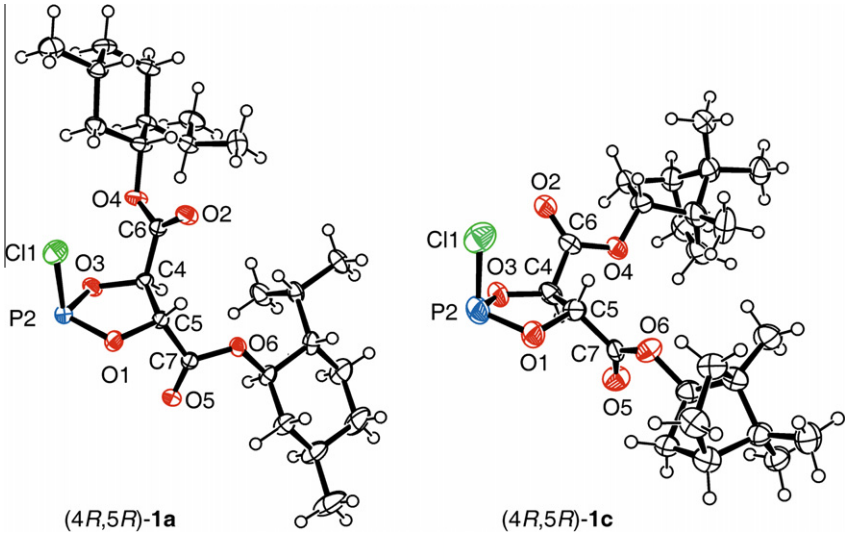


Figure 3. Ellipsoid graphics (50% probability level) of 2-chloro-1,3,2-dioxaphospholanes (4*R*,5*R*)-**1a** (left) and (4*R*,5*R*)-**1c** (right) in the solid state (150 K; hydrogen atoms were depicted as circles of an arbitrary radius).

Table 2
Selected solid state parameters of menthyl chlorodioxaphospholane (4*R*,5*R*)-**1a** and borneyl derivative (4*R*,5*R*)-**1c**

Entry	parameter (Å) or (°)	(4*R*,5*R*)-**1a**	(4*R*,5*R*)-**1c**
1	O1–P2	1.601 (1)	1.630 (4)
2	P2–O3	1.617 (2)	1.605 (4)
3	P2–Cl1	2.105 (1)	2.089 (3)
4	Cl1–P2–O1–C5	−85.5 (1)	−74.4 (4)
5	Cl1–P2–O3–C4	79.8 (1)	84.8 (4)

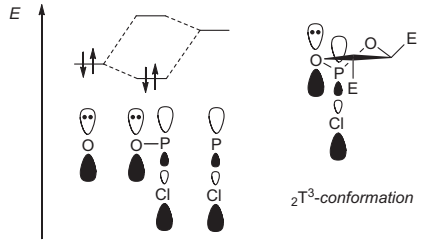


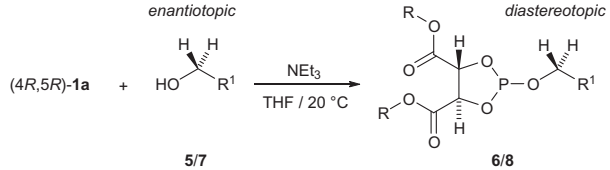
Figure 4. Proposed model for the conformational stabilization of 2-chloro-1,3,2-dioxaphospholanes **1a**–**d** via $p^2(O)\rightarrow\sigma^*(P,Cl)$ delocalization (E = ester substituent).

phosphite formation on the chemical shift for the oxygen bonded carbon in alcohol **5** is small ($\Delta\delta = -1.4$ ppm; Table 3). In the phosphorus NMR, the conversion of (4*R*,5*R*)-**1a** into phosphite **6** leads to an upfield shift of 30.3 ppm (Tables 1 and 3). Since esterification of benzyl alcohol **7** with (4*R*,5*R*)-**1a** provides a similar shift and multiplicity change, we can conclude that *O*-benzyl phosphite **8** is formed under such conditions (Table 3, entry 2).

Esterification of (*R*)-phenylethanol (*R*)-**9** and enantiomer (*S*)-**9** (both >97:3 er) with chlorodioxaphospholane (4*R*,5*R*)-**1a** provides diastereomers (*R*)-**10** and (*S*)-**10**. Proton (600 MHz) and carbon (151 MHz) NMR-shift differences of the phosphites were too small to serve as a basis for quantitative analysis (Table 4). A shift dispersion of 1.3 ppm, on the other hand, is sufficiently large enough for baseline separation of the phosphorus resonances of (*R*)-**10** and (*S*)-**10** for quantitative analysis.

The quantitative in situ conversion of α-phenylethanol **9** into phosphite **10** for NMR-analysis requires mixing chlorodioxaphospholane (4*R*,5*R*)-**1a** (1.2 equiv) from a stock solution in chloroform-d_1, an alcohol (c_0 ~0.2 M), and a slight excess of

Table 3
Yields and NMR-data of trialkylphosphites prepared from prochiral alcohols



Entry	**5**/**7** (R^1)	**6**/**8**[a] (%)	δ_H ($J_{P,C}$/Hz)[b]	δ_C (J/Hz)[c]	δ_P[c]
1	**5** (CCl_3)	**6**/quant.	4.25 dd (11.8, 7.2)[c] 4.38 dd (11.8, 8.2)[c]	75.1 d (13.9)	144.3
2	**7** (C_6H_5)	**8**/92	4.70 dd (12.5, 7.6)[d] 4.76 dd (12.5, 7.9)[d]	65.5 d (12.9)	143.9

[a] ^{31}P NMR ($OPPh_3$ as the internal standard; for R see Fig. 1).
[b] ($J_{P,H}$, $J_{H,H}$).
[c] In $CDCl_3$.
[d] In C_6D_6.

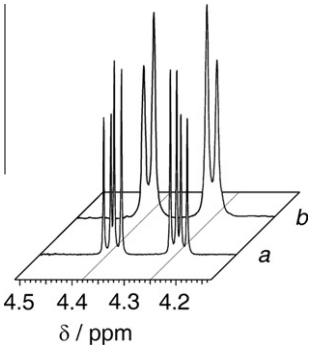
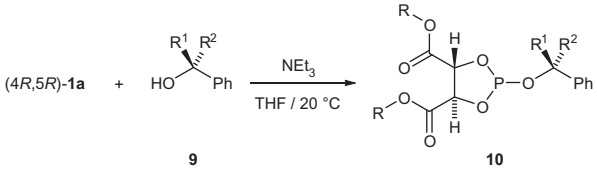


Figure 5. Excerpt of phosphorus-coupled (*a*) and -decoupled (*b*) ^{1}H NMR-spectra of trichloroethyl phosphite **6**.

triethylamine (c_0 ~0.2 M) in an NMR-tube. Phosphite formation occurs instantaneously, as can be seen from the upfield shift of ~30 ppm in the phosphorus NMR-spectrum. A second phosphorus resonance which is often found at 130 ppm originates from the phosphonium salt formation by substituting triethylamine for chloride in (4*R*,5*R*)-**1a**.

Table 4
Yields and NMR-data for trialkylphosphites prepared from α-phenylethanol **9**



Entry	**9**	R^1	R^2	**10**[a] (%)	δ_H (J/Hz)[b,c]	δ_C ($J_{P,C}$/Hz)[b]	δ_P [c]
1	(*R*)-**9**	H	CH_3	(*R*)-**10**: 94	5.24 dq (8.4, 6.6)	72.7 d (18.0)	145.7
2	(*S*)-**9**	CH_3	H	(*S*)-**10**: 99	5.24 dq (8.4, 6.5)	72.8 d (15.3)	144.4

[a] ^{31}P NMR ($OPPh_3$ as the internal standard; for R see Fig. 1).
[b] ($J_{P,H}$, $J_{H,H}$).
[c] In $CDCl_3$.

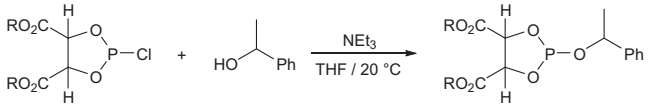
2.4. Assessment of 2-chloro-1,3,2-dioxaphospholanes

To investigate the role of the terpenyl group on the degree of the phosphorus NMR shift dispersion, menthyl-, borneyl-, and fenchyl-substituted chlorodioxaphospholanes **1a–d** were esterified with racemic phenylethanol **9** in almost quantitative yields (Table 5). The reactions, which furnished phosphites, showed baseline-separated phosphorus resonances being dispersed by 1.3–2.3 ppm (Table 5). The separation of phosphite resonances was effected by relative configuration and constitution of the monoterpenyl entity (Table 5, entries 1 and 3 or 2 and 4).

To find an agent suitable for determining the enantiomeric purity of a more representative set of alcohols, which are typically encountered in stereoselective synthesis, we esterified the racemates of primary alcohols **11–13** (stereocenters at the β- or γ-position), secondary substrates **14–15** (open chain and cyclic), and tertiary derivative **16** with chlorodioxaphospholanes **1a–d** (Tables 6 and 7).

From the grid of 6 (chlorodioxaphospholanes) × 6 (alcohols), (36 data points) we concluded that the effect of the ester group in **1** is significant but small (Tables 6 and 7). In cases where the shift dispersions of diastereomeric phosphites prepared from (4*R*,5*R*)-**1b** were small or not resolved (Tables 6 and 7, entry 3), the separation of signals was found in esterifications starting from (4*R*,5*R*)-**1a** (Tables 6 and 7, entry 1). Steric encroachment in proximity of the hydroxyl group has a similarly small but important effect on the phosphorus NMR-shift dispersion, which was more pronounced for the cyclic secondary substrate **14** and less for primary substrates **11–13** and tertiary alcohol **16**. Since shift dispersions of 0.2 ppm are enough to obtain baseline separated signals, we selected compound (4*R*,5*R*)-**1a** for further study with a precision analysis (Section 2.5) and a structure-shift dispersion correlation for alcohols that are relevant for ongoing projects (Section 2.6).

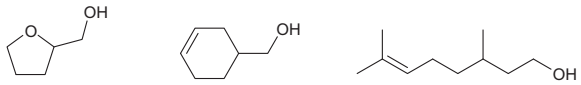
Table 5
Formation of 2-alkoxy-1,3,2-dioxaphospholanes



Entry	**1**	Yield[a] (%)	Products (δ ^{31}P/ppm) [b]	$\Delta\delta$
1	(4*R*,5*R*)-**1a**	98	145.4/144.0	1.4
2	(4*S*,5*S*)-**1b**	97	145.4/144.1	1.4
3	(4*R*,5*R*)-**1b**	97	145.2/142.9	2.3
4	(4*S*,5*S*)-**1a**	98	145.2/142.9	2.3
5	(4*R*,5*R*)-**1c**	96	145.8/143.8	2.0
6	(4*R*,5*R*)-**1d**	95	146.4/144.4	2.0

[a] In $CDCl_3$, referenced versus $OPPh_3$ as the internal standard.
[b] Referenced versus 85% H_3PO_4 in a sealed capillary as an external standard.

Table 6
Chemical shift of phosphites formed from primary alcohols



(±)-**11** (±)-**12** (±)-**13**

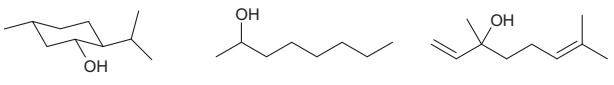
Entry	**1**	(±)-**11** δ[a] (ppm)	(±)-**12** δ[a] (ppm)	(±)-**13** δ[a] (ppm)
1	(4*R*,5*R*)-**1a**	145.1/144.9	143.9/143.8	143.9/143.7
2	(4*S*,5*S*)-**1b**	145.0/144.7	143.8/143.7	143.9/143.7
3	(4*R*,5*R*)-**1b**	142.8/142.7	142.0/141.8	141.4/141.3
4	(4*S*,5*S*)-**1a**	142.7/142.6	141.9/141.8	141.2/141.1
5	(4*R*,5*R*)-**1c**	143.8/143.5	142.6/142.5	142.8/142.7
6	(4*R*,5*R*)-**1d**	143.9/143.7	143.2/143.1	142.6/142.5

[a] Prepared from equimolar amounts of **1a–d** and **11–13** in dry THF/$CDCl_3$ = 2:1 (v/v) at 20 °C in an NMR-tube (referenced versus 85% H_3PO_4 in a sealed capillary as the external standard).

2.5. Precision for the analysis of enantiomeric purity

Mixtures of enantiomers (*R*)-**9** and (*S*)-**9** afforded diastereomers of phosphite **10** in yields between 95% and 98%, if treated with chlorodioxaphospholane (4*R*,5*R*)-**1a** (Table 8). Integration of the phosphorus resonances originating from diastereomeric phosphites reflected the enantiomeric ratios of known (*R*)-**9**/(*S*)-**9**-compositions with a precision of ±1%. We believe that this precision is representative for the method, as long as the yield of trialkyl phosphites is close to quantitative and the enantiomeric ratio does not exceed the precision of the NMR-method.

Table 7
Chemical shifts of phosphites formed from secondary and tertiary alcohols

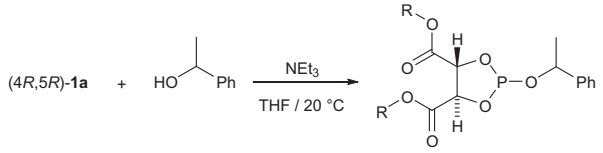


(±)-**14** (±)-**15** (±)-**16**

Entry	**1**	(±)-**14** δ_P[a] (ppm)	(±)-**15** δ_P[a] (ppm)	(±)-**16** δ_P[a] (ppm)
1	(4*R*,5*R*)-**1a**	145.3/144.6	144.9/144.7	143.6/143.5
2	(4*S*,5*S*)-**1b**	145.3/144.9	144.9/144.7	143.6/143.5
3	(4*R*,5*R*)-**1b**	145.4	143.6	145.1/144.9
4	(4*S*,5*S*)-**1a**	145.5	143.7	145.1/144.9
5	(4*R*,5*R*)-**1c**	145.8/145.2	144.2/144.1	144.8/144.7
6	(4*R*,5*R*)-**1d**	146.2/145.4	145.0/144.9	146.4/146.3

[a] Prepared from equimolar amounts of **1a–d** and **14–16** in dry THF/$CDCl_3$ = 2:1 (v/v) at 20 °C in an NMR-tube (referenced versus 85% H_3PO_4 in a sealed capillary as the external standard).

Table 8
2-(1-Phenylethyl-1-oxy)-1,3,2-dioxaphospholane syntheses



Entry	(*R*)-**9**:(*S*)-**9**	**10**[a] (%)	(*R*)-**10**:(*S*)-**10**
1	>97:3	95	>98:2
2	95:5	98	96:4
3	47:53	95	47:53
4	5:95	96	5:95
5	<3:97	95	<2:98

[a] Versus $OPPh_3$ as internal standard via ^{31}P NMR; R = [(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohex-1-yl]oxycarbonyl.

2.6. Correlating structure and shift dispersion

Chiral alkyl-, alkenyl-, and alkynyl-substituted alcohols play an important role as substrates for natural product synthesis via oxidative transformations, and, therefore, were chosen to explore the effect of steric branching and unsaturation on phosphorus NMR-shift dispersion in (4*R*,5*R*)-**1a**-derived phosphites (Fig. 6).

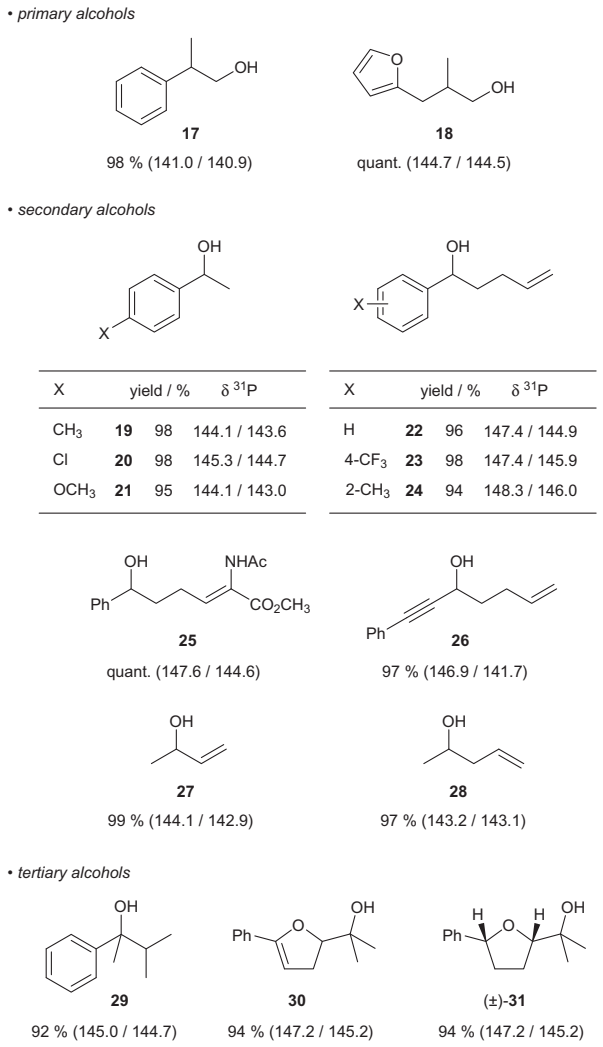


Figure 6. Yields [in percent, via phosphorus NMR, except for **25**-derived phosphite (proton NMR)] and phosphorus NMR-shifts (numbers in parentheses) of diastereomeric phosphites prepared from racemic alcohols **17**–**31**.

Racemic primary, secondary, and tertiary alcohols **17**–**31** afforded phosphites in yields between 92% and quantitative, if treated with (4*R*,5*R*)-**1a** and triethylamine (for conditions, see Section 2.4 and the Experimental). The phosphorus resonances of the phosphites were between 141.0 ppm and 148.3 ppm. The degree of shift dispersions increased along the sequence of phosphites obtained from primary alcohols **17** and **18**[35] via secondary alcohol **28**, tertiary alcohols **29**–**31**,[36,37] allylic alcohol **27,** benzylic alcohols **19**–**25**[38–43] to propargylic alcohol **26**.[44] The shifts of the diastereomeric phosphites prepared from (4*R*,5*R*)-**1a** and alkenol **25**, which is a precursor for the synthesis of non naturally occurring amino acids via oxidative transformations, for example were dispersed by 3 ppm as shown in Figure 7.

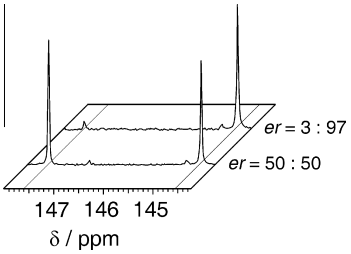


Figure 7. Excerpt from phosphorus NMR-spectra (243 MHz) for enantiomer analysis of alkenol **25** via (4*R*,5*R*)-**1a**-derived phosphites.

Compounds **17**–**31** pose as a selection of reagents which reflect our own interests and thus may not be regarded as fully representative. The results derived from this study, however, show that substrates with a π-system bound to the α-carbon of the alcohol (cf. **19**–**27**) of cyclic secondary and/or structurally biased alcohols (**14**, **30**, **31**) generally lead to shift dispersions that are sufficiently large enough to allow baseline separation of diastereomeric phosphites. The fact that both enantiomers of tertiary heterocyclic alcohols **30** and **31** provide, in a similar manner, well separated phosphorus resonances upon derivatizing with (4*R*,5*R*)-**1a**, is an important result at the end of this study, because side chain-functionalized tetrahydrofurans are a major target in our laboratory.[45,46]

3. Conclusion

Chlorodioxaphospholane (4*R*,5*R*)-**1a** is a versatile derivatizing agent for quantifying the enantiomeric purity of chiral alcohols via phosphorus-31 NMR-spectroscopy. We believe that there is a demand to use the agent as an analytical tool, and also for purposes other than those listed herein, such as routine analysis or mechanistic investigation. The arguments to use the agent are (i) low cost, (ii) synthetic access, (iii) ease of application, and (iv) precision.

(i) *Low costs*. (*R*,*R*)-Tartaric acid and (1*R*,2*S*,5*R*)-menthol are inexpensive chemicals, which are available from the chiral pool and thus from renewable resources. The price of phosphorus trichloride compares well to the price of thionyl chloride. Thionyl chloride and the more expensive oxalyl chloride, are generally used to convert α-methoxy-α-trifluoromethylphenyl acetic acid, (Mosher's acid)[13] into the derived acid chloride, which is required to derivatize chiral alcohols for stereochemical analysis.

(ii) *Synthetic access*. The synthetic method developed herein allows us to prepare 10–26 g of chlorodioxaphospholane (4*R*,5*R*)-**1a** in a single batch. We see no inherent limitation for scaling up the process further, since work-up and purification occurs by distillation and crystallization, and not by chromatography.

(iii) *Ease of application*. Storage of neat (4*R*,5*R*)-**1a** in standard glassware being exposed to air is possible without decomposition of the agent over a reasonable time scale. However, we recommend to store stock solutions, as used in routine NMR-analysis, in an atmosphere of dry argon or nitrogen. Derivatization of alcohols in solution occurs almost instantaneously and quantitatively by mixing with (4*R*,5*R*)-**1a** and triethylamine.

(iv) *Precision*. Esterification of (4*R*,5*R*)-**1a** with racemic primary, secondary, and tertiary alcohols gives diastereomeric phosphites, showing in the majority of investigated instances phosphorus NMR-shift dispersions of 0.2 ppm and more, which is enough to achieve baseline separation with the 243 MHz NMR-spectrometer used. The enantiomeric ratios of alcohols determined differed from the diastereomeric ratios of phosphites by one percent or less, which is sufficient for most applications.

We have used chlorodioxaphospholane (4*R*,5*R*)-**1a** for about four years to determine the enantiomeric purity of a variety of alcohols, such as thermally labile, hydroxyl-substituted oxygen radical precursors, products of enzyme-catalyzed alcohol desymmetrization, or chiral hydroxyl-substituted cyclic ethers as building blocks for natural products, to mention the most important examples.[21,47,20] For us, the agent and the method described herein has become the standard tool to determine the enantiomeric purity of chiral alcohols.

4. Experimental

4.1. General

Melting points (°C) were determined on an Electrothermal A9100 instrument and are uncorrected. Combustion analysis was performed on a 2400 CNH (*Perkin Elmer*). ^{1}H, ^{13}C and ^{31}P spectra were recorded with DPX 200, and DPX 600 spectrometers (*Bruker*). The resonances of residual protons and of carbons from deuterated solvent molecules $CDCl_3$ (δ_H 7.26, δ_C 77.16), C_6D_6 (δ_H 7.16, δ_C 128.06) served as internal standard. ^{31}P NMR spectra were referenced versus 85% (w/w) aq H_3PO_4 ($\delta = 0$) as external standard. Reaction progress was monitored by thin layer chromatography on aluminum plates coated with silica gel (60 F_{254}, *Merck*). Products were detected by UV-spotting (254 nm) or with anisaldehyde/H_2SO_4/EtOH, that is, Ekkert's reagent. All synthetic manipulations associated with the synthesis of chlorodioxaphospholanes **1a**–**d** were performed in an atmosphere of dry argon in oven-dried (T = 110 °C) glassware.

4.2. 2-Chloro-1,3,2-dioxaphospholanes from alkyl tartrates

4.2.1. General method

A solution of dialkyl tartrate **2a**–**d** in dry THF was added at 20 °C to a solution of PCl_3 (3.9 or 7.8 equiv) in the same solvent. The solution was stirred for 1 h at 65 °C. After cooling to 20 °C, the solvent and excess phosphorus trichloride were removed under reduced pressure. The residual oil was taken up in dry pentane (volume see below) and kept at −20 °C (for at least 6–24 h). The crystals, that were separated from the solution, were collected, and dried under reduced pressure to furnish analytically pure 2-chloro-1,3,2-dioxaphospholane **1a**–**d**.

4.2.2. 2-Chloro-(4*R*,5*R*)-bis{[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohex-1-yl]oxycarbonyl}-1,3,2-dioxaphospholane (4*R*,5*R*)-1a

From bis{[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohex-1-yl]oxycarbonyl}-(*R*,*R*)-tartrate (*R*,*R*)-**2a**[23] (6.29 g, 14.8 mmol), PCl_3 (15.8 g, 115 mmol), and THF (10 mL for the tartrate solution, 10 mL for the PCl_3 solution). Crystallization of the crude oil from pentane (10 mL) at −20 °C furnished 6.33 g (12.9 mmol, 87%) of compound (4*R*,5*R*)-**1a** as a colorless solid. Mp 72 °C. $[\alpha]_D^{25} = -155.0$ (*c* 1.00, THF). ^{1}H NMR (C_6D_6, 600 MHz) δ 0.58 (qd, J_d = 3.5, J_q = 9.4 Hz, 1H), 0.59 (qd, J_d = 3.5, J_q = 9.4 Hz, 1H), 0.70 (d, J = 6.6 Hz, 3H), 0.71 (d, J = 6.6 Hz, 3H), 0.74 (d, J = 7.0 Hz, 3H), 0.75 (d, J = 7.0 Hz, 3H), 0.72–0.77 (m, 2H), 0.78 (d, J = 7.0 Hz, 3H), 0.82 (d, J = 7.0 Hz, 3H), 0.89 (q, J = 11.2 Hz, 1H), 1.02 (q, J = 10.9 Hz, 1H), 1.04–1.12 (m, 2H), 1.36–1.43 (m, 6H), 1.90–2.05 (m, 4H), 4.85 (td, J_d = 4.4, J_t = 10.7 Hz, 1H), 4.95 (td, J_d = 4.6, J_t = 10.7 Hz, 1H), 5.07 (dd, J = 7.0, 8.6 Hz, 1H), 5.69 (d, J = 7.0 Hz, 1H). ^{13}C NMR (C_6D_6, 151 MHz) δ 16.2, 16.3, 20.8, 20.9, 22.0 (2C), 23.4, 23.5, 26.4, 26.5, 31.32, 31.34, 34.1, 34.2, 40.5, 40.6, 47.0, 47.1, 76.9, 77.0, 77.7 (d, J = 8.3 Hz), 78.8 (d, J = 9.7 Hz), 166.6 (d, J = 5.6 Hz), 167.0. ^{31}P NMR (C_6D_6, 162 MHz) δ 175.6. Anal. Calcd for $C_{24}H_{40}ClO_6P$: C, 58.71; H, 8.2. Found: C, 58.55; H, 8.26. Crystals suitable for X-ray diffraction were grown by slow evaporation from a saturated solution of (4*R*,5*R*)-**1a** in dry pentane. X-ray crystallography: $C_{24}H_{40}ClO_6P$, T = 150(2) K, λ = 0.71073 Å, monoclinic, $P2_1$, a = 5.5810(2) Å, b = 15.0739(7) Å, 15.9350(6) Å, β = 95.224(4)°, Z = 2, μ = 0.237 mm^{-1}, completeness to 2θ = 89.1%, goodness-of-fit on F^2 = 0.975, final R indices [$I > 2\sigma(I)$]: R_1 = 0.0389, wR_2 = 0.0832.

4.2.3. 2-Chloro-(4*S*,5*S*)-bis{[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohex-1-yl]oxycarbonyl}-1,3,2-dioxaphospholane (4*S*,5*S*)-1a

From bis{[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohex-1-yl]oxycarbonyl}-(*S*,*S*)-tartrate (*S*,*S*)-**2a**[23] (9.40 g, 22.0 mmol), PCl_3 (11.7 g, 85.7 mmol), and THF (20 mL for the tartrate solution, 10 mL for the PCl_3 solution). Crystallization of the crude oil from pentane (30 mL) at −20 °C furnished 7.80 g (15.9 mmol, 72%) of compound (4*S*,5*S*)-**1a** as a colorless solid. Mp 69–71 °C. $[\alpha]_D^{25} = +21.3$ (*c* 1.00, THF). ^{1}H NMR (C_6D_6, 600 MHz) δ 0.57 (qd, J_d = 3.7, J_q = 13.0 Hz, 1H), 0.59 (qd, J_d = 3.7, J_q = 13.0 Hz, 1H), 0.69 (d, J = 6.4 Hz, 3H), 0.72 (d, J = 6.6 Hz, 3H), 0.73–0.76 (m, 2H), 0.77 (d, J = 6.8 Hz, 3H), 0.79 (d, J = 6.8 Hz, 3H), 0.81 (d, J = 6.6 Hz, 3H), 0.85 (d, J = 7.0 Hz, 3H), 0.89 (q, J = 11.6 Hz, 1H), 0.90 (q, J = 11.6 Hz, 1H), 1.03–1.11 (m, 2H), 1.29–1.44 (m, 6H), 1.88–2.00 (m, 3H), 1.94 (septd, J_d = 2.9, J_{sept} = 7.0 Hz, 1H), 1.96–2.00 (m, 1H), 2.14 (septd, J_d = 2.9 Hz, J_{sept} = 7.0 Hz, 1H), 4.88 (tdd, J_d = 2.6, 4.4, J_t = 10.7 Hz, 2H), 5.06 (dd, J = 7.5, 8.3 Hz, 1H), 5.70 (d, J = 7.2 Hz, 1H). ^{13}C NMR (C_6D_6, 151 MHz) δ 16.2, 16.4, 20.7, 20.9, 22.0 (2C), 23.3, 23.5, 26.1, 26.5, 31.3 (2C), 34.1, 34.2, 40.6, 40.7, 47.1, 47.2, 77.0, 77.1, 77.6 (d, J = 8.3 Hz), 78.8 (d, J = 8.3 Hz), 166.6 (d, J = 5.5 Hz), 167.0. ^{31}P NMR (C_6D_6, 162 MHz) δ 175.5. Anal. Calcd for $C_{24}H_{40}ClO_6P$: C, 58.71; H, 8.21. Found: C, 58.44; H, 8.32.

4.2.4. 2-Chloro-(4*S*,5*S*)-bis{[(1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohex-1-yl]oxycarbonyl}-1,3,2-dioxaphospholane (4*S*,5*S*)-1b

From bis{[(1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohex-1-yl]oxycarbonyl}-(*S*,*S*)-tartrate (*S*,*S*)-**2b**[23] (19.5 g, 45.7 mmol), PCl_3 (24.4 g, 178 mmol), and THF (40 mL for the tartrate solution, 20 mL for the PCl_3 solution). Crystallization of the crude oil from pentane (50 mL) at −20 °C furnished 19.7 g (40.1 mmol, 88%) of compound (4*S*,5*S*)-**1b** as a colorless solid. Mp 70–71 °C. $[\alpha]_D^{25} = +151.4$ (*c* 1.00, THF). ^{1}H NMR (C_6D_6, 600 MHz) δ 0.59 (qd, J_d = 3.5, J_q = 9.4 Hz, 1H), 0.60 (qd, J_d = 3.5, J_q = 9.4 Hz, 1H), 0.71 (d, J = 6.6 Hz, 3H), 0.72 (d, J = 6.6 Hz, 3H), 0.74 (d, J = 7.0 Hz, 3H), 0.76 (d, J = 7.0 Hz, 3H), 0.75–0.79 (m, 2H), 0.81 (d, J = 7.0 Hz, 3H), 0.82 (d, J = 7.0 Hz, 3H), 0.88 (q, J = 12.1 Hz, 1H), 1.00 (q, J = 11.4 Hz, 1H), 1.04–1.12 (m, 2H), 1.28–1.43 (m, 6H), 1.87–2.03 (m, 4H), 4.83 (td, J_d = 4.4, J_t = 10.7 Hz, 1H), 4.91 (td, J_d = 4.4, J_t = 10.7 Hz, 1H), 5.04 (t, J = 8.6 Hz, 1H), 5.64 (d, J = 7.0 Hz, 1H).

^{13}C NMR (C_6D_6, 151 MHz) δ 16.2, 16.3, 20.8 (2C), 22.0 (2C), 23.4, 23.5, 26.4, 26.5, 31.3 (2C), 34.1, 34.2, 40.5, 40.6, 47.0, 47.1, 76.9, 77.0, 77.7 (d, J = 8.3 Hz), 78.8 (d, J = 8.3 Hz), 166.6 (d, J = 4.2 Hz), 167.0. ^{31}P NMR (C_6D_6, 162 MHz) δ 175.6. Anal. Calcd for $C_{24}H_{40}ClO_6P$: C, 58.71; H, 8.21. Found: C, 58.67; H, 8.18.

4.2.5. 2-Chloro-(4*R*,5*R*)-bis{[(1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohex-1-yl]oxycarbonyl}-1,3,2-dioxaphospholane (4*R*,5*R*)-1b

From bis{[(1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohex-1-yl]oxycarbonyl}-(*R*,*R*)-tartrate (*R*,*R*)-**2b**[23] (9.20 g, 21.6 mmol), PCl_3 (11.5 g, 84.2 mmol), and THF (20 mL for the tartrate solution, 10 mL for the PCl_3 solution). Crystallization of the crude oil from pentane (20 mL) at −20 °C furnished 8.25 g (16.8 mmol, 78%) of compound (4*R*,5*R*)-**1b** as a colorless solid. Mp 67–68 °C. $[\alpha]_D^{25} = -20.6$ (*c* 1.00, THF). ^{1}H NMR (C_6D_6, 600 MHz) δ 0.57 (qd, J_d = 3.5, J_q = 12.1 Hz, 1H), 0.59 (qd, J_d = 3.5, J_q = 12.1 Hz, 1H), 0.70 (d, J = 6.6 Hz, 3H), 0.71 (d, J = 6.6 Hz, 3H), 0.73–0.76 (m, 2H), 0.74 (d, J = 6.6 Hz, 3H), 0.77 (d, J = 7.0 Hz, 3H), 0.81 (d, J = 7.0 Hz, 3H), 0.85 (d, J = 7.0 Hz, 3H), 0.89 (q, J = 11.6 Hz, 1H), 0.91 (q, J = 11.6 Hz, 1H), 1.05–1.13 (m, 2H), 1.28–1.44 (m, 6H), 1.88–1.92 (m, 1H), 1.94 (td, J_d = 2.9, J_t = 7.0 Hz, 1H), 1.96–2.00 (m, 1H), 2.14 (septd, J_d = 2.9, J_{sept} = 7.0 Hz, 1H), 4.87 (tdd, J_d = 1.1, 4.4, J_t = 10.7 Hz, 2H), 5.05 (dd, J = 7.5, 8.3 Hz, 1H), 5.69 (d, J = 7.2 Hz, 1H). ^{13}C NMR (C_6D_6, 151 MHz) δ 16.2, 16.4, 20.7, 20.9, 22.0 (2C), 23.3, 23.5, 26.1, 26.5, 31.3 (2C), 34.1, 34.2, 40.6, 40.7, 47.1, 47.2, 77.0, 77.1, 77.6 (d, J = 8.3 Hz), 78.8 (d, J = 8.3 Hz), 166.6 (d, J = 5.5 Hz), 167.0. ^{31}P NMR (C_6D_6, 162 MHz) δ 175.5. Anal. Calcd for $C_{24}H_{40}ClO_6P$: C, 58.71; H, 8.21. Found: C, 58.56; H, 8.31.

4.2.6. 2-Chloro-(4*R*,5*R*)-bis{[(1*S*,2*R*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]oxycarbonyl}-1,3,2-dioxaphospholane (4*R*,5*R*)-1c

From bis{[(1*S*,2*R*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]oxycarbonyl}-(*R*,*R*)-tartrate (*R*,*R*)-**2c**[23] (3.10 g, 7.34 mmol), PCl_3 (7.82 g, 57.3 mmol), and THF (40 mL for the tartrate solution, 40 mL for the PCl_3 solution). Crystallization of the crude oil from pentane (6 mL) at −20 °C furnished 2.88 g (5.91 mmol, 81%) of compound (4*R*,5*R*)-**1c** as a colorless solid. Mp 82 °C. $[\alpha]_D^{25} = -105$ (*c* 1.00, THF). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.85 (s, 3H), 0.87 (s, 3H), 0.89 (s, 3H), 0.92 (s, 3H), 1.05 (dd, J = 3.3, 14.0 Hz, 1H), 1.10 (dd, J = 3.3, 13.8 Hz, 1H), 1.23–1.30 (m, 2H), 1.32–1.37 (m, 2H), 1.69–1.80 (m, 4H), 1.91 (ddd, J = 4.4, 9.4, 13.4 Hz, 1H), 1.99 (ddd, J = 4.4, 9.4, 13.6 Hz, 1H), 2.35–2.44 (m, 2H), 4.98 (dd, J = 6.8, 9.1 Hz, 1H), 5.00–5.06 (m, 2H), 5.43 (d, J = 6.7 Hz, 1H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 13.5, 13.6, 18.8 (2C), 19.6 (2C), 27.0 (2C), 27.1, 27.8, 27.9, 36.1, 36.5, 44.8 (2C), 48.0, 48.1, 49.0, 77.1 (d, J = 9.7 Hz), 78.3 (d, J = 8.6 Hz), 83.0, 83.1, 167.3 (d, J = 4.8 Hz), 167.7. ^{31}P NMR (C_6D_6, 162 MHz) δ 175.6. Anal. Calcd for $C_{24}H_{36}ClO_6P$: C, 59.20; H, 7.45. Found: C, 59.57; H, 7.49. Crystals suitable for X-ray diffraction were grown by slow evaporation from a saturated solution of (4*R*,5*R*)-**1c** in dry pentane. X-ray crystallography: $C_{24}H_{36}ClO_6P$, T = 150(2) K, λ = 1.54184 Å, orthorhombic, $P2_12_12_1$, a = 9.6077(5) Å, b = 13.4396(6) Å, c = 19.3284(14) Å, Z = 4, μ = 2.264 mm^{-1}, completeness to 2θ = 93.1%, goodness-of-fit on F^2 = 1.105, final R indices [$I > 2\sigma(I)$]: R_1 = 0.0578, wR_2 = 0.1244.

4.2.7. 2-Chloro-(4*R*,5*R*)-bis{[(1*R*,2*R*,4*S*)-1,3,3-trimethylbicyclo[2.2.1]hept-2-yl]oxycarbonyl}-1,3,2-dioxaphospholane (4*R*,5*R*)-1d

From bis{[(1*R*,2*R*,4*S*)-1,3,3-trimethylbicyclo[2.2.1]hept-2-yl]oxycarbonyl} (*R*,*R*)-tartrate (*R*,*R*)-**2d**[23] (3.10 g, 7.34 mmol), PCl_3 (7.82 g, 57.3 mmol), and THF (20 mL for the tartrate solution, 20 mL for the PCl_3 solution). Crystallization of the crude oil from pentane (10 mL) at −20 °C furnished 2.99 g (6.14 mmol, 84%) of compound (4*R*,5*R*)-**1d** as a colorless solid. Mp 80 °C. $[\alpha]_D^{25} = -17.0$ (*c* 1.00, THF). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.81 (s, 3H). 0.84 (s, 3H), 1.06 (s, 3H), 1.07 (s, 3H), 1.09–1.18 (m, 2H), 1.12 (s, 3H), 1.13 (s, 3H), 1.20–1.26 (m, 2H), 1.43–1.54 (m, 2H), 1.57–1.62 (m, 2H), 1.65–1.83 (m, 6H), 4.48–4.52 (m, 2H), 5.00 (dd, J = 7.1, 8.7 Hz, 1H), 5.49 (d, J = 7.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 19.3, 19.4, 20.1, 20.2, 25.7, 25.8, 25.8, 26.4, 26.5, 29.6 (2C), 39.6, 39.8, 41.3, 41.4, 48.2, 48.3, 48.6 (2C), 77.2 [superposition of the central signal from the 1/1/1-triplet from the solvent prevents resolution of the $^2J_{P,C}$-coupling; in C_6D_6: δ_C 77.6, ^2J = 8.3 Hz], 78.2 (d, J = 8.6 Hz), 89.0 (2C), 167.3 (d, J = 5.0 Hz), 167.7. ^{31}P NMR (C_6D_6, 243 MHz) δ 175.3. Anal. Calcd for $C_{24}H_{36}ClO_6P$: C, 59.20; H, 7.45. Found: C, 59.28; H, 7.38.

4.3. Preparation of alcohols

4.3.1. Methyl (6*S*)-2-acetylamino-6-hydroxy-6-phenylhex-2-enoate (*S*)-25

To a mixture of lipase [*Aspergillus niger* lipase (187 U/g)] (491 mg) and phosphate-buffer (395 mL) [pH 7, 0.1 M aq KH_2PO_4 (500 mL), 0.1 M aq NaOH (290 mL), and H_2O (210 mL)] was added (±)-1-phenylpent-4-en-1-ylacetate (4.81 g, 23.5 mmol). The reaction mixture was stirred for 6 days at 40 °C, then saturated with NaCl and extracted with Et_2O (4 × 50 mL). The combined organic layers were washed with brine (50 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure. The remaining oil was purified by column chromatography [R_f = 0.28, SiO_2, petroleum ether/EtOAc = 5:1 (v/v)], to afford (1*S*)-1-phenylpent-4-en-1-ol as a colorless liquid. Yield: 1.39 g (8.57 mmol, 36%). $[\alpha]_D^{20} = -14.6$ (*c* 1.03, EtOH). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.76–1.94 (m, 2H), 1.96 (br s, 1H), 2.04–2.22 (m, 2H), 4.70 (t, J = 6.5 Hz, 1H), 4.98–5.07 (m, 2H), 5.80–5.90 (m, 1H), 7.26–7.31 (m, 1H), 7.35–7.36 (m, 4H). (1*S*)-1-Phenylpent-4-en-1-ol (649 mg, 4.00 mmol) was dissolved in CH_3CN (20 mL) and $RuCl_3 \times xH_2O$ (28.7 mg) was added at 22 °C. The mixture was treated with H_2O (3 mL) and $NaIO_4$ (1.71 g, 8.00 mmol) was added over a period of 5 min. The resulting mixture was stirred for 45 min at 22 °C, then treated with satd aq $Na_2S_2O_3$ (10 mL) and H_2O (100 mL). The solution was extracted with CH_2Cl_2 (3 × 50 mL). The organic layer was washed with brine (50 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure, to give (5*S*)-phenyltetrahydrofuran-2-ol (299 mg, 1.82 mmol) as a colorless oil. This material was added at 22 °C to a solution of methyl-2-(acetylamino)-2-(dimethylphosphoryl)acetate[48] (478 mg, 2.00 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (304 mg, 2.00 mmol) in dry THF (7.5 mL), which had been prepared at −78 °C and stirred for 2 h at that temperature. The reaction mixture was stirred for 45 min at 22 °C and then diluted with EtOAc (10 mL). The organic phase was separated and washed with satd aq NH_4Cl (2 × 15 mL). The aqueous layer was extracted with EtOAc (2 × 15 mL). The combined organic solutions were washed with brine (15 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure. The remaining oil was purified by column chromatography [R_f = 0.33, SiO_2, EtOAc]. Yield: 205 mg (0.74 mmol, 41%), colorless oil. $[\alpha]_D^{25} = +10.0$ (*c* 1.00, EtOH). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.87–1.96 (m, 2H), 2.08 (s, 3H), 2.26–2.30 (m, 1H), 2.33–2.39 (m, 1H), 3.12 (br s, 1H), 3.76 (s, 3H), 4.65–4.67 (m, 1H), 6.66 (t, J = 7.7 Hz, 1H), 7.20 (br s, 1H), 7.23–7.25 (m, 1H), 7.31–7.33 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.1, 25.1, 37.3, 73.0, 125.6 (2C), 125.7, 127.3, 128.3 (2C), 137.9, 144.3, 165.0, 169.2.

4.3.2. Methyl (±)-2-acetylamino-6-hydroxy-6-phenylhex-2-enoate (±)-25

Methyl-2-(acetylamino)-2-(dimethylphosphoryl)acetate (718 mg, 3.00 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (457 mg,

3.00 mmol), and 5-phenyltetrahydrofuran-2-ol (493 mg, 3.00 mmol) were converted as described in Section 4.3.1. Yield: 275 mg (0.99 mmol, 33%), yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.89–1.98 (m, 2H), 2.11 (s, 3H), 2.26–2.42 (m, 2H), 2.92 (br s, 1H), 3.78 (s, 3H), 4.67–4.70 (m, 1H), 6.70 (t, J = 7.7 Hz, 1H), 7.07 (br s, 1H), 7.27–7.28 (m, 1H), 7.31–7.35 (m, 4H).

4.3.3. 1-(4-Trifluoromethylphenyl)-pent-4-en-1-ol 23

1-(4-Trifluoromethylphenyl)-pent-4-en-1-ol was prepared from 4-trifluoromethylphenyl carbaldehyde (9.58 g, 55.0 mmol) and but-3-enyl magnesium bromide from 4-bromo-1-butene (7.43 g, 55.0 mmol) and magnesium turnings (1.46 g, 60.1 mmol) in Et_2O (30 mL) according to a published procedure.[49] Yield: 7.35 g (31.9 mmol, 58%), colorless oil. Bp 123 °C (12 mbar). R_f = 0.23 for petroleum ether/EtOAc = 2:1 (v/v). ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.77–1.96 (m, 2H), 2.06 (d, J = 3.4, 1H, OH), 2.10–2.21 (m, 2H), 4.73–4.79 (m, 1H), 4.98–5.10 (m, 2H), 5.83 (ddt, J_d = 10.4, 17.1, J_t = 6.7 Hz, 1H), 7.46 (d, J = 8.5 Hz, 2H), 7.60 (d, J = 8.5 Hz, 2H). ^{13}C NMR ($CDCl_3$ 63 MHz) δ 30.3, 38.6, 73.8, 115.4, 125.7, 126.54, 130.1 (q, $J_{C,F}$ = 30.5 Hz), 138.2, 148.9, 148.9, 149.0. Anal. Calcd for $C_{12}H_{13}F_3O$: C, 62.60; H, 5.69. Found: C, 62.43; H, 5.82.

4.3.4. 2-(5-Phenyl-2,3-dihydrofur-2-yl)-propan-2-ol 30

A solution of ethyl [5-(2-hydroxyprop-2-yl)-2-phenyl]-4,5-dihydrofuran-3-carboxylate[50] (276 mg, 1.00 mmol) in NaOH (0.5 M, 50 mL) was stirred for 18 h at 24 °C and allowed to rest for 48 h. The pH of the mixture was adjusted to 2–3 with aq HCl [10% (w/w)]. The organic products were extracted with Et_2O (3 × 50 mL) from this solution. The combined organic washings were extracted with H_2O (50 mL) and brine (50 mL). The organic solution was dried (Na_2SO_4) and concentrated under reduced pressure to give a colorless oil. This material was dissolved in Et_2O (2 mL) and pentane (2 mL). The solution was allowed to rest at −20 °C. The precipitate was collected by filtration and dried to give 5-(2-hydroxyprop-2-yl)-2-phenyl-4,5-dihydrofuran-3-carboxylic acid. Yield: 120 mg (0.48 mmol, 59%), colorless crystals. Mp 129–131 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.25 (s, 3H), 1.33 (s, 3H), 3.04 (dd, J = 9.5, 15.1 Hz, 1H), 3.09 (dd, J = 10.8, 15.5 Hz, 1H), 4.61 (dd, J = 9.5, 10.4 Hz, 1H), 7.36–7.41 (m, 2H), 7.42–7.46 (m, 1H), 7.78 (dd, J = 1.5, 7.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 23.7, 25.5, 32.3, 71.9, 88.1, 102.2, 127.8, 129.4, 129.5, 130.7, 166.8, 169.2. IR (KBr) $\tilde{\nu}$ cm^{-1} 3311, 2984, 2627, 1667, 1636, 1593, 1570, 1493, 1446, 1380, 1347, 1324, 1273, 1232, 1174. Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 68.17; H, 6.84. An oven-dried, 10 mL-microwave vial was charged with 5-(2-hydroxyprop-2-yl)-2-phenyl-4,5-dihydrofuran-3-carboxylic acid (248 mg, 1.00 mmol), Cu_2O (7.15 mg, 0.05 mmol), dry NMP (1.5 mL), dry quinoline (0.5 mL), and 4,7-diphenyl-1,10-phenanthroline (33.2 mg, 0.10 mmol). The resulting mixture was placed for 15 min in a modomode microwave instrument (CEM Discover®) and heated with 150 W microwave power to 190 °C. The mixture was concentrated under reduced pressure and purified by chromatography [SiO_2, Et_2O/pentane = 1:1 (v/v)]. 2-(5-Phenyl-2,3-dihydrofur-2-yl)-propan-2-ol. Yield: 63 mg (0.31 mmol, 31%), pale yellow oil. R_f = 0.51 [Et_2O/pentane = 1:1 (v/v)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.32 (s, 3H), 1.38 (s, 3H), 1.83 (br s, 1H), 2.23 (dt, J_t = 4.4, J_d = 18.2 Hz, 1H), 2.53 (ddd, J = 18.1, 4.8, 3.5 Hz, 1H), 3.64–3.71 (m, 1H), 5.23 (t, J = 4.1 Hz, 1H), 7.23–7.36 (m, 3H), 7.57–7.58 (dd, J = 1.6, 8.6 Hz, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 22.1, 24.2, 28.3, 69.7, 77.3, 93.2, 124.7, 128.0, 128.1, 136.1, 149.6. IR (NaCl) $\tilde{\nu}$ cm^{-1} 3428, 2974, 2926, 2853, 1719, 1684, 1652, 1599, 1494, 1448, 1380, 1367, 1324, 1154. Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.43; H, 8.17.

4.4. Formation of phosphites

4.4.1. General method

In a NMR tube, a solution (250 μl) containing an alcohol (0.2 M) and NEt_3 (0.25 M) in $CDCl_3$ was treated with a solution (300 μl) of 2-chloro-1,3,2-dioxaphospholane (4*R*,5*R*)-**1a** (0.2 M) and $OPPh_3$ (0.2 M) in $CDCl_3$. The NMR tube was shaken and subjected to NMR-spectroscopy. The specified yields were determined via ^{31}P NMR against $OPPh_3$ as the internal standard.

4.4.2. Esterification of 1,1,1-trichloroethanol 5

Yield: quant. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.71 (d, J = 7.0 Hz, 6H), 0.80–0.89 (m, 14H), 0.93–1.07 (m, 4H), 1.36–1.49 (m, 4H), 1.61–1.69 (m, 4H), 1.76–1.88 (m, 2H), 1.97 (dt, J_t = 4.8, J_d = 12.2 Hz, 2H), 4.25 (dd, J = 7.3, 11.7 Hz, 1H), 4.38 (dd, J = 8.1, 11.8 Hz, 1H), 4.70–4.81 (m, 3H), 5.10 (d, J = 6.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.2, 21.0, 22.1, 23.3, 26.3, 31.5, 34.2, 40.7, 40.8, 46.9, 75.1 (d, J = 14.1 Hz), 76.3 (d, J = 9.3 Hz), 76.8, 76.9, 77.3 (d, J = 8.3 Hz), 96.6 (d, J = 5.6 Hz), 167.7, 167.8 (d, J = 5.6 Hz). ^{31}P NMR (243 MHz, $CDCl_3$) δ 144.3.

4.4.3. Esterification of benzylalcohol 7

Yield: 92%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.66 (d, J = 7.0 Hz, 3H), 0.70 (d, J = 7.0 Hz, 3H), 0.77–0.87 (m, 14H), 0.93–1.06 (m, 4H), 1.36–1.49 (m, 4H), 1.58–1.67 (m, 4H), 1.76–1.88 (m, 3H), 1.96 (dt, J_t = 5.1, J_d = 11.7 Hz, 1H), 4.70–4.79 (m, 4H), 4.86 (dd, J = 8.6, 12.9 Hz, 1H), 5.08 (d, J = 5.9 Hz, 1H), 7.19–7.32 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 15.9, 16.0, 20.8, 21.9, 23.1, 26.1, 31.4, 34.0, 40.4, 40.5, 46.8, 65.0 (d, J = 13.0 Hz), 76.1 (d, J = 9.3 Hz), 76.4, 76.5, 77.1 (d, J = 10.2 Hz), 127.1, 127.8, 128.4, 137.3 (d, J = 5.6 Hz), 168.0, 168.1 (d, J = 5.6 Hz). ^{31}P NMR (243 MHz, $CDCl_3$) δ 143.9.

4.4.4. Esterification of (*R*)-1-phenylethan-1-ol (*R*)-9

Yield: 94%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.68 (d, J = 7.0 Hz, 3H), 0.71 (d, J = 6.8 Hz, 3H), 0.81–0.85 (m, 14H), 0.91–1.05 (m, 4H), 1.36–1.43 (m, 4H), 1.45 (d, J = 6.5 Hz, 3H), 1.59–1.66 (m, 4H), 1.77 (septd, J_d = 2.6, J_{sept} = 7.0 Hz, 1H), 1.84 (septd, J_d = 2.9, J_{sept} = 7.0 Hz, 1H), 1.91–1.97 (m, 2H), 4.66 (dd, J = 8.4, 6.3 Hz, 1H), 4.71 (td, J_d = 4.6, J_t = 10.9 Hz, 1H), 4.78 (td, J_d = 4.6, J_t = 10.9 Hz, 1H), 5.03 (d, J = 6.2 Hz, 1H), 5.21 (dq, J_q = 6.6, J_d = 8.4 Hz, 1H), 7.28–7.16 (m, 5H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 15.9, 16.0, 20.8, 21.9, 23.1, 25.2, 26.0, 26.1, 31.3, 34.0, 40.5, 40.6, 46.7, 46.8, 72.7 (d, J = 18.0 Hz), 75.6 (d, J = 8.3 Hz), 76.3, 76.4, 77.0 (d, J = 9.7 Hz), 125.6, 127.6, 128.4, 142.9 (d, J = 2.8 Hz), 167.9, 168.1 (d, J = 4.2 Hz). ^{31}P NMR (243 MHz, $CDCl_3$) δ 145.7.

4.4.5. Esterification of (*S*)-1-phenylethan-1-ol (*S*)-9

Yield: 92%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.70 (d, J = 6.8 Hz, 3H), 0.71 (d, J = 7.0 Hz, 3H), 0.79–0.87 (m, 14H), 0.88–1.05 (m, 4H), 1.27–1.39 (m, 4H), 1.45 (d, J = 6.5 Hz, 3H), 1.61–1.66 (m, 4H), 1.74–1.89 (m, 3H), 1.93–1.98 (m, 1H), 4.65 (dd, J = 8.5, 6.5 Hz, 1H), 4.73 (td, J_d = 4.5, J_t = 10.8 Hz, 1H), 4.77 (td, J_d = 4.4, J_t = 10.6 Hz, 1H), 5.03 (d, J = 6.5 Hz, 1H), 5.24 (dq, J_q = 6.5, J_d = 8.4 Hz, 1H), 7.28–7.17 (m, 5H). ^{13}C NMR (243 MHz, $CDCl_3$) δ 16.0, 16.1, 20.8, 21.9, 23.1, 25.5, 26.1, 31.3, 34.0, 40.4, 40.5, 46.7, 46.8, 72.8 (d, J = 15.3 Hz), 75.6 (d, J = 8.3 Hz), 76.3, 76.4, 77.1 (d, J = 9.7 Hz), 125.5, 127.6, 128.3, 143.0 (d, J = 2.8 Hz), 168.0, 168.1 (d, J = 5.6 Hz). ^{31}P NMR (243 MHz, $CDCl_3$) δ 144.4.

Crystallographic data (excluding structure factors) for the structures herein have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication [CCDC 814031 for (4*R*,5*R*)-**1a**, and CCDC 814032 for (4*R*,5*R*)-**1c**]. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union

Road, Cambridge CB2 1EZ, UK, (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

Acknowledgments

This investigation was supported by the state Rheinland-Pfalz (Landesgraduiertenstipendium for G.S. and scholarship of the Stipendienstiftung des Landes for M.A.). This work is part of Ph.D. theses of M.A., I.K., and G.S.

References

1. Kolb, H. C.; van Nieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547.
2. Hartung, J.; Greb, M. *J. Organomet. Chem.* **2002**, *661*, 67–84.
3. Wolfe, J. P.; Hay, M. B. *Tetrahedron* **2007**, *63*, 261–290.
4. Nógrádi, M. *Stereoselective Synthesis*, 2nd ed.; VCH: Weinheim, 1995.
5. Parker, D. *Chem. Rev.* **1991**, *91*, 1441–1457.
6. Raban, M.; Mislow, K. *Tetrahedron Lett.* **1965**, *6*, 4249–4253.
7. Pirkle, W. H.; Beare, S. D. *J. Am. Chem. Soc.* **1969**, *91*, 5150–5155.
8. Whitesides, G. M.; Lewis, D. W. *J. Am. Chem. Soc.* **1970**, *92*, 6979–6980.
9. Schurig, V.; Nowotny, A. P. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 939–959.
10. Allenmark, S. G. *Chromatographic Enantioseparation: Methods and Applications*; Ellis Horwood: Chichester, 1988.
11. Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512–519.
12. Secon, J. M.; Quiñoá, E.; Riguera, R. *Chem. Rev.* **2004**, *104*, 17–117.
13. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543–2549.
14. Anderson, R. C.; Shapiro, M. J. *J. Org. Chem.* **1984**, *49*, 1304–1305.
15. Alexakis, A.; Mutti, S.; Mangeney, P. *J. Org. Chem.* **1992**, *57*, 1224–1237.
16. Brunel, J.-M.; Pardigon, O.; Maffei, M.; Buono, G. *Tetrahedron: Asymmetry* **1992**, *3*, 1243–1246.
17. Hulst, R.; de Vries, N. K.; Feringa, B. L. *Tetrahedron: Asymmetry* **1994**, *5*, 669–708.
18. *Phosphorus-31 NMR Spectral Properties in Compound Characterization and Structural Analysis*; Quin, L. D., Verkade, J. G., Eds.; VCH: Weinheim, 1994.
19. Berger, S.; Braun, S.; Kalinowski, H.-O. In *NMR-Spektroskopie von Nichtmetallen*; Thieme: Stuttgart, 1993; Vol. 3, Chapter 1.
20. Schuch, D.; Fries, P.; Dönges, M.; Hartung, J. *J. Am. Chem. Soc.* **2009**, *131*, 12918–12920.
21. Amberg, M.; Bergsträsser, U.; Stapf, G.; Hartung, J. *J. Org. Chem.* **2008**, *73*, 3907–3910.
22. Amberg, M.; Bergsträsser, U.; Stapf, G.; Hartung, J. *J. Org. Chem.* **2008**, *73*, 6052.
23. Egli, M.; Dobler, M. *Helv. Chim. Acta* **1989**, *72*, 1136–1150.
24. Fuchs, B., Ed.Topics in Stereochemistry; Eliel, E. L., Allinger, N. L., Eds.; Wiley: New York, 1978; Vol. 10, pp 1–94.
25. Hedberg, K.; Iwasaki, M. *J. Chem. Phys.* **1962**, *36*, 589–591.
26. Cattani-Lorente, M.; Geoffroy, M.; Mishra, S. P.; Weber, J.; Bernadinelli, G. *J. Am. Chem. Soc.* **1986**, *108*, 7148–7153.
27. Kumar, K. V. P. P.; Swamy, K. C. K. *Carbohydr. Res.* **2007**, *342*, 1182–1188.
28. Sood, P.; Koutha, M.; Fan, M.; Klichko, Y.; Zahng, H.; Lattman, M. *Inorg. Chem.* **2004**, *43*, 2975–2980.
29. Kop-Weiershausen, T.; Lex, J.; Neudorfl, J.-M.; Goldfuss, B. *Beilstein J. Org. Chem.* **2005**, *1*, 6.
30. Naumov, V. A.; Dakkouri, M.; Naumov, A. V. *Russ. J. Gen. Chem.* **2001**, *71*, 1024–1029.
31. Kirby, A. J. *Stereoelectronic Effects*; Oxford Science Publications: Oxford, 1996. pp 13–23.
32. Bentrude, W. G. In *Phosphorus-31 NMR Spectral Properties in Compound Characterization and Structural Analysis*; Quin, L. D., Verdade, J. G., Eds.; VCH: Weinheim, 1994; pp 41–53.
33. Besserre, D.; Coffi-Nketsia, S. *Org. Magn. Reson.* **1980**, *13*, 313–318.
34. Pouchoulin, G.; Llinas, J. R.; Buono, G.; Vincent, E. J. *Org. Magn. Reson.* **1976**, *8*, 518–521.
35. Fuganti, C.; Grasselli, P.; Servi, S.; Högberg, H.-E. *J. Chem. Soc., Perkin Trans. 1* **1988**, 3061–3065.
36. Driver, T. G.; Harris, J. R.; Woerpel, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 3836–3837.
37. Hartung, J.; Drees, S.; Greb, M.; Schmidt, P.; Svoboda, I.; Fuess, H.; Murso, A.; Stalke, D. *Eur. J. Org. Chem.* **2003**, 2388–2408.
38. Hartung, J. *Eur. J. Org. Chem.* **2001**, 619–632.
39. Barry, C. N.; Evans, S. A. *J. Org. Chem.* **1981**, *46*, 3361–3364.
40. Savile, C. K.; Kazlauskas, R. J. *J. Am. Chem. Soc.* **2005**, *127*, 12228–12229.
41. Mowry, D. T.; Renoll, M.; Huber, W. F. *J. Am. Chem. Soc.* **1946**, *68*, 1105–1109.
42. Wang, C.; Kingsbury, C. A. *J. Org. Chem.* **1972**, *37*, 2489–2494.
43. Olah, G. A.; Porter, R. D.; Kelly, D. P. *J. Am. Chem. Soc.* **1971**, *93*, 464–466.
44. Weber, B.; Seebach, D. *Tetrahedron* **1994**, *50*, 7473–7481.
45. Hartung, J.; Drees, S.; Geiss, B.; Schmidt, P. *Synlett* **2003**, 223–226.
46. Hartung, J. *Pure Appl. Chem.* **2005**, *77*, 1559–1574.
47. Hartung, J.; Kempter, I.; Gottwald, T.; Kneuer, R. *Tetrahedron: Asymmetry* **2009**, *20*, 2097–2104.
48. Davies, S. G.; Rodríguez-Solla, H.; Tamayo, J. A.; Cowley, A. R.; Concellón, C.; Garner, A. C.; Parkes, A. L.; Smith, A. D. *Org. Biomol. Chem.* **2005**, *3*, 1435–1447.
49. Hartung, J.; Hiller, M.; Schmidt, P. *Liebigs Ann. Chem.* **1996**, 1425–1436.
50. Antonioletti, R.; Righi, G.; Oliveri, L.; Bovicelli, P. *Tetrahedron Lett.* **2000**, *41*, 10127–10130.