[5]HELOL Phosphite: A Helically Grooved Sensor of Remote Chirality

Daniel J. Weix, Spencer D. Dreher, and Thomas J. Katz*

Contribution from the Department of Chemistry, Columbia University, New York, New York 10027

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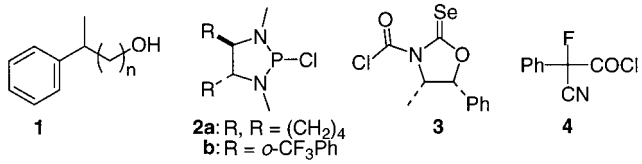
Abstract: Even when the first center of chirality is far from a functional group, the stereochemistries of chiral molecules can be sensed if the functional group is attached to a phosphorus embedded within the groove of a nonracemic helicene. The sensor used was a phosphite ester of [5]HELOL, structure **6**, and ^{31}P NMR spectroscopy was the method of analysis. Although there are seven methylenes between the hydroxyl and the first center of chirality, the ^{31}P NMRs could distinguish the enantiomers of 8-phenylnonanol with baseline resolution. However, to achieve this resolution, the solvent has to be chosen appropriately. The probe can also analyze the enantiomers of other alcohols, amines, phenols, and, when they were coupled to 2-aminophenol, carboxylic acids. The sensitivity to remote chiral centers of the moieties analyzed is attributed to their confinement to the helical groove.

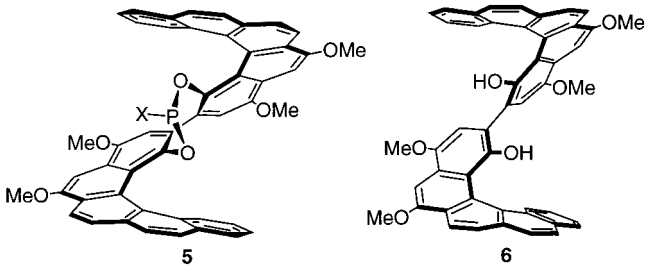
Introduction

Although the chiral purities of enantiomeric mixtures can be analyzed by a number of chromatographic[1] or NMR spectroscopic methods,[2] when the centers of chirality are remote from reactive functional groups, the analyses fail. For example, the (*R*)- and (*S*)-enantiomers of **1** for *n* up to 2 can be distinguished because the ^{31}P, ^{77}Se, and ^{19}F NMR chemical shifts of the esters they form with **2a**, **3**, and **4** differ significantly.[3,4] However, there is no indication that similar analyses succeed when $n > 2$.[5] The detection limits of HPLC analyses using chiral solid phases are only slightly better. A support in which (*aR*)-1,1′-bianthracene-2,2′-dicarboxylic acid is bound to silica gel separates the enantiomers of **1** ($n = 3$),[6] but there is no indication that it or any chiral support can when $n > 3$.

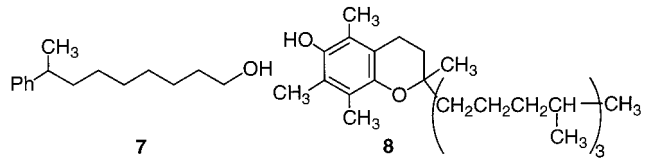


1 **2a**: R, R = $(CH_2)_4$ **b**: R = *o*-CF_3Ph **3** **4**

We speculated that the sensitivity to remote chiral centers could be increased if a ^{31}P probe used for NMR analyses were embedded in a large chiral groove, as in structure **5**. In such a structure, chiral centers of X, even those distant from the point at which X is attached to the phosphorus, could experience significant diastereomeric interactions. Since **5** (X = Cl) should form when **6** is combined with PCl_3, since **5** gives the same



product whether nucleophiles displace the chlorine with retention or inversion, and since nonracemic **6**, which we called [5]-HELOL, is easy to prepare in appreciable amounts,[7] we tested whether this reagent could be used to analyze the enantiomeric purities of molecules whose centers of chirality are far from their functional groups. The results reported here include the discovery that when [5]HELOL chlorophosphite (**5**, X = Cl) is used as a chiral derivatizing agent (CDA), the range of alcohols of structure **1** that can be analyzed is extended enormously: from the previous limit, $n = 3$, to $n = 7$. The reagent can analyze the enantiomeric purity of structure **7**! It can distinguish the enantiomers of a number of alcohols, amines, and, with the aid



7 **8**

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(4) Takeuchi, Y.; Itoh, N.; Satoh, T.; Koizumi, T.; Yamaguchi, K. *J. Org. Chem.* **1993**, *58*, 1812. These authors showed that reagent **4** is better than the related one of Mosher, which is barely effective when $n = 2$.

(5) In fact, **2b**, which is a good probe of enantiomeric excess in other cases, fails for **1** ($n = 2$). See: Alexakis, A.; Frutos, J. C.; Mutti, S.; Mangeney, P. *J. Org. Chem.* **1994**, *59*, 3326.

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of a linker not previously used for this purpose, carboxylic acids, substances for whose analysis—surprisingly, considering how common they are—only a few CDAs have previously been designed.[8] In addition, we report how altering the solvents can significantly improve the sensitivity of the analyses.

Results

Following Alexakis,[5] the reagent for the analysis, **5** (X = Cl), was prepared as needed. The procedure, which is a variant of ones used for 1,1′-binaphthalene-2,2′-diol[9] and for the amine-precursors of **2a** and **2b**,[5] combines **6** and a small amount of 4-(dimethylamino)pyridine (DMAP) with a solution of PCl_3 in CH_2Cl_2 and Et_3N. The material to be analyzed is then added, followed by $CDCl_3$. The solvent can also be replaced and analyses then carried out when the samples are dissolved in, for example, CD_3CN. The transformations cleanly gave **5** (X = OR* or NHR*), and when the reactant was (±)-2-methylbutanol, the product (**5** with X = $OCH_2CHEtMe$) was isolated, purified by chromatography, and characterized. Like related phosphite esters,[3a,10] the [5]HELOL phosphites were difficult to purify, presumably because they react quickly with water and oxygen in the air. However, we could isolate a sample in excellent yield (87%) whose ^{1}H NMR spectrum showed resonances for aromatic, methoxy, and alkyl protons in the required intensity ratio and whose mass spectrum showed the mass of the parent peak correctly. Moreover, the strongest peak in its IR spectrum, at 906 cm^{-1}, is characteristic of phosphite esters,[11] as are the next most intense peaks, at 731, 789, 738, and 835 cm^{-1}.[11,12] There are peaks at 1164 and 1213 cm^{-1}, where aryl phosphites absorb,[11,13] but their intensity is only medium. The ^{31}P NMR spectrum, analyzed with proton decoupling, consists of two peaks, at δ 131.97 and 131.88 ppm relative to external 85% H_3PO_4, chemical shifts expected for the phosphite structure.[14] The ratio of their intensities was 0.98:1.

As summarized in Tables1−4, the ratios of the diastereomers formed by the other materials analyzed could be determined similarly by ^{31}P NMR spectroscopy, but because the phosphorus derivatives react with air and because the analyses were not improved by it, the samples were not purified before the spectra were recorded. In every one of more than 30 cases, the diastereomeric excesses (de's) equaled within 3% the enantiomeric excesses (ee's) of the materials analyzed.[15] Even 4,4′-dimethylbenzoin, a molecule that is crowded about the alcohol group, gave its diastereomers without the amount of either being noticeably enriched. If DMAP was omitted from the procedure, the transformations were not clean, and the ratios in which the diastereomers of **5** (X = OR* or NHR*) were formed sometimes did not equal the ratios of the enantiomers derivatized. All the spectra show, in addition to the peaks for **5**, a ^{31}P resonance at −1 ppm, attributable to the diarylphosphonate.[14a] The intensity of this peak was small if the $CDCl_3$ had been filtered through basic alumina.

The instrument used for the analyses was a 300 MHz ^{1}H NMR spectrometer. Although it depends on the line widths, the instrument resolved the ^{31}P resonances of diastereomers to

Table 1. Differences between the ^{31}P Chemical Shifts ($\Delta\delta$, in ppm) of the Diastereomers **5** (X = OR*) that Are Formed by Alcohols $CH_3CHR(CH_2)_nOH$, R = Ph and Et (Solvents Are Either $CDCl_3$ or CD_3CN)

	R = Ph		R = Et
n	in $CDCl_3$	in CD_3CN	in $CDCl_3$
0	0.74		
1	1.37		0.087
2	0.30		0.43
3	0.21		0.20
4	0.32		0.043
5	0.27		*a*
6	0.018[b]	0.15	
7	0.027[b]	0.070	
8	*a*		

[a] Unresolvable in either solvent. [b] Not baseline resolved.

Table 2. Differences between the ^{31}P Chemical Shifts ($\Delta\delta$) of the Diastereomers **5** (X = NHR*) Formed by Amines

amine	$\Delta\delta$ (ppm)[a]
1-phenylethylamine	0.77
1-(1-naphthyl)ethylamine	0.30
sec-butylamine	0.81
2-phenylpropylamine	0.38
1-aminoindan	2.45
2-(2-aminoethyl)-1-methyl-pyrrolidine	0.91

[a] The solvent was $CDCl_3$.

Table 3. Differences between the ^{31}P Chemical Shifts ($\Delta\delta$) of the Diastereomers **5** (X = OR*) Formed by Some Alcohols and Phenols (R*OH)

R*OH	$\Delta\delta$ (ppm)[a]
1-phenylbut-3-en-1-ol	2.29
1-indanol	3.21
4,4′-dimethylbenzoin	8.05
4-*sec*-butylphenol	0.59
vitamin E (**8**)	0.21
β-citronellol (3,7-dimethyl-6-octenol)	0.32

[a] The solvent was $CDCl_3$.

Table 4. Differences between the ^{31}P Chemical Shifts ($\Delta\delta$, in ppm) of the Diastereomers **9** that Are Formed by Carboxylic Acids $CH_3CHPh(CH_2)_nCO_2H$ and How They Change with Solvent

n	in $CDCl_3$	in other solvents
1	0.96	
2	1.83	
3	0.42	
4	0.19[a]	0.26[b,c]
5	0.076[a]	0.16[d]
6	*a*	0.021[d,e]

[a] Unresolvable. [b] In Et_2O with a very small amount of $CDCl_3$ to provide a lock signal. [c] $\Delta\delta$ = 0.11 when the solvent was CD_3CN. [d] In CD_3CN. [e] Not baseline resolved.

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(10) (a) Reference 2b, p 124. (b) Said, M. A.; Swamy, K. C. K.; Veith, M.; Huch, V. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2945.

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(12) Daimay, L.-V.; Colthup, N. B.; Fateley, W. G.; Grasselli, J. G. *The Handbook of Infrared and Raman Characteristic Frequencies of Organic Molecules*; Academic Press: New York, 1991; pp 270−273.

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(15) Three percent is approximately the accuracy of the NMR analyses.

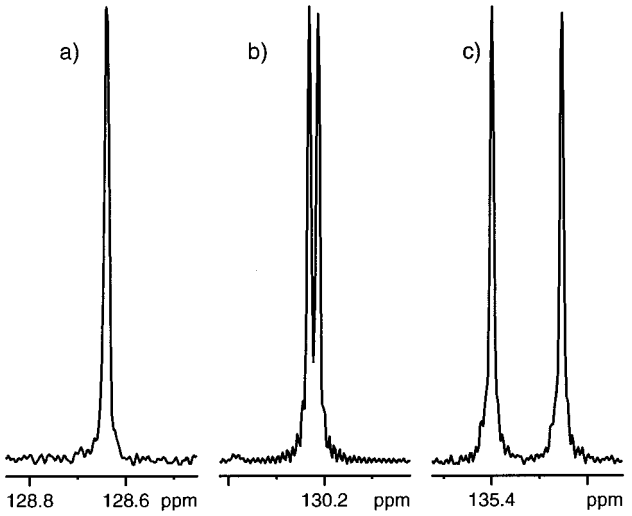


Figure 1. ^{31}P NMRs of **5** [X = $O(CH_2)_6CHPhCH_3$] in (a) ether with a small amount of $CDCl_3$ added to provide a frequency lock signal, (b) $CDCl_3$, and (c) CD_3CN.

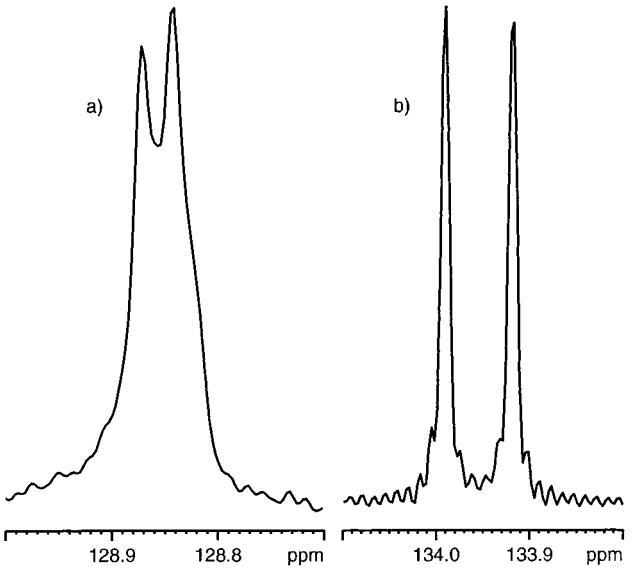
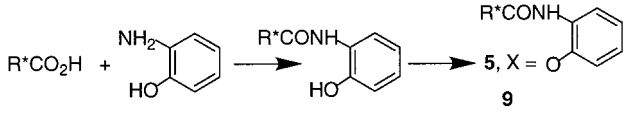


Figure 2. ^{31}P NMRs of **5** [X = $O(CH_2)_7CHPhCH_3$] in (a) $CDCl_3$ and (b) CD_3CN.

Scheme 1



the baseline when peaks were as little as 0.04 ppm apart. As Table 1 shows, this means that the derivatives of **1** could be analyzed in $CDCl_3$ solution even when $n = 3$, 4, or 5. Moreover, as Table 1 and Figures1 and 2 show, when the solvent was changed to CD_3CN, the analysis could be extended to **1** even when $n = 6$ and 7.

The analyses were applied not only to alcohols $CH_3CHR(CH_2)_nOH$ (R = Ph and C_2H_5, Table 1) but also to amines (Table 2), to various other alcohols, and to phenols such as 4-(2-butyl)-phenol and vitamin E (**8**, Table 3). The application to phenols in turn suggested a way to analyze carboxylic acids (Scheme 1): to couple them with a rigid linker, 2-aminophenol, and to analyze the resulting 2-amidophenols, **9**, like other phenols, after they had been coupled to **5** (X = Cl). Table 4 shows the analyses. The carboxylic acids that were precursors to alcohols

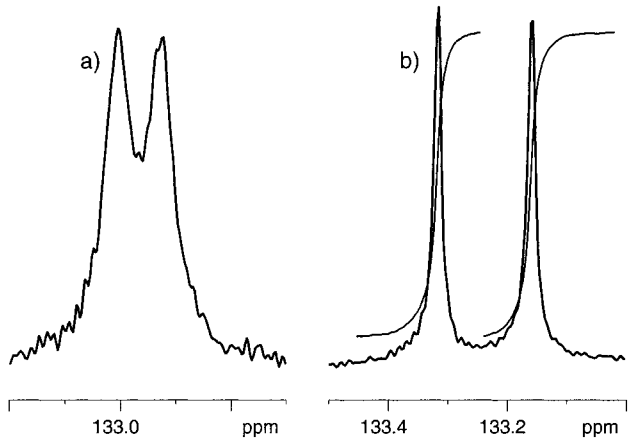


Figure 3. ^{31}P NMRs of **9** [R*CO = $CH_3CHPh(CH_2)_5CO$] in (a) $CDCl_3$ and (b) CD_3CN.

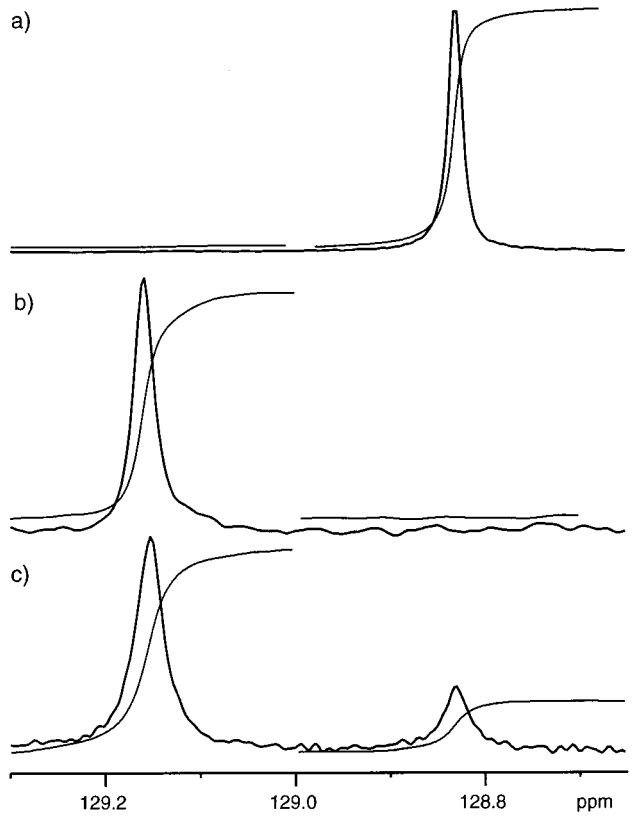


Figure 4. ^{31}P NMRs of **5** [X = $O(CH_2)_2CHMe(CH_2)_3CH{=}CMe_2$] in $CDCl_3$: (a) prepared from (*R*)-*β*-citronellol, (b) prepared from (*S*)-*β*-citronellol, and (c) a mixture comprised of 19.4% of the (*R*)-isomer and 80.6% of the (*S*)-isomer, that is, with an ee of 61.2%. The ee found according to the spectra displayed is 60.5%.

1 could be analyzed in $CDCl_3$ solution up to $n = 3$ (5-phenylhexanoic acid). However, as in the case of the alcohols, the analyses could be extended to $n = 4$ (6-phenylheptanoic acid) and to $n = 5$ (7-phenyloctanoic acid) when other solvents were used: diethyl ether plus $CDCl_3$ for the former and CD_3CN for the latter. Figure 3 shows how the distinction between the two diastereomers of **9** (R*CO = 7-phenyloctanoyl) improves when the solvent is changed from $CDCl_3$ to CD_3CN.

To test the ability of **5** to analyze the composition of mixtures of enantiomers, samples of *β*-citronellol (3,7-dimethyl-6-octenol) were analyzed. Figure 4 displays the ^{31}P NMR spectra of the phosphite esters of (*M*,*M*)-**5** and each of the following: (*S*)-*β*-citronellol, (*R*)-*β*-citronellol, and a mixture of the two whose

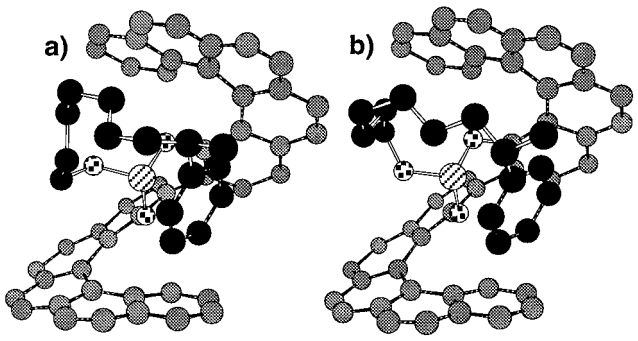


Figure 5. Conformations of minimum energy of (*M*,*M*)-**5** with X = $O(CH_2)_7CHPhMe$ when the side chain has (a) the (*R*)-configuration and (b) the (*S*)-configuration. Hydrogens and methoxyl groups have been deleted for clarity. Oxygen atoms are shown as speckled and phosphorus as striped.

ee was 61.2 ± 0.1% [the (*S*)-isomer predominating].[16] The analyses show the (*S*)-β-citronellol to be >98% enantiomerically pure, the (*R*)-β-citronellol to be >98% enantiomerically pure, and the ee of the mixture to be 60.3 ± 2%. These data also show that the enantiomeric purity of the [5]HELOL reagent was ≥98%.

To analyze why **5** is effective in distinguishing the stereochemistry of remote chiral centers, calculations were made to find the conformations of lowest energy for the two diastereomers of **5** in which X was $O(CH_2)_7CHPhMe$. The Macromodel V.6.0 program[17] with AMBER* force field,[18] operating on a Silicon Graphics-O2 computer, was used for the conformational searches. Initially, a structure of local minimum energy was calculated for **5** (X = $O(CH_2)_7CHPhMe$) in the selected solvent. The structure was then subjected to a Metropolis Monte Carlo conformational search using the standard parameters in Macromodel. No parts of the molecule were constrained. The conformations of lowest energy found for the two diastereomers are displayed in Figure 5.

The results of these calculations showed that in the conformation of globally minimum energy, the (*R*) alkoxy chain lies within the cleft of the helicene whether the solvent is water or chloroform. When water was the selected solvent, all the other conformations within 2 kcal/mol of the global minimum (there were two) were also folded like this. However, when the solvent was chloroform, 40% of the other conformations within 2 kcal/mol of the global minimum (there were five) had the alkoxy chain extended, with the phenyl and methyl groups outside the cleft.[19]

Discussion

The data in Tables 1−4 imply that [5]HELOL chlorophosphite (**5**, X = Cl), presumably because it binds molecules within a helical groove, is by far the most sensitive probe there is for remote chirality. When combined with alcohols of structure **1**, it extends the ability to distinguish configurations of chiral centers from the previous limit, $n = 3$, to $n = 7$. For the methylalkanols $Et(Me)CH(CH_2)_nOH$, it extends the limit from $n = 3$ to $n = 4$.[20,21]

It also analyzes carboxylic acids. Three points are significant in this regard. The first is that reagent **5** is effective, for it is one of very few reported for the analyses of chiral acids.[8] Second is that of the few previously studied reagents, only one has been reported to distinguish chiral centers that are remote from the carboxyl group.[8b,22] Although the compounds tested before are different from those tested here, Table 4 shows that reagent **5** distinguishes chiral centers that are even further from the carboxyl than the furthest analyzed before. The situation is similar when chromatographic methods are considered.[23] Third is that the linker used here, 2-aminophenol, or related linkers have not previously been used as auxiliaries with other reagents that analyze alcohols and amines. The linker is short and should therefore keep the attached centers of chirality within or near the groove of the [5]HELOL ligand.

The mechanism by which the phosphorus atom distinguishes the chirality of the remote centers is not known, but the three-point rule[26] implies that the distinction, when for example molecules **1** are bonded to **5**, originates from the relationships between both the remote phenyl and methyl groups and the helical structure. A model in which $O(CH_2)_8CH_3$ in its all-trans extended conformation is bonded to **5** (at X) was constructed by means of the Macromodel computer program. It shows that at least the first three carbon atoms must lie within the [5]HELOL groove. Substituents even on the fourth carbon must interact with the [5]HELOL skeleton, and if the chain either does not point straight out along [5]HELOL's C_2 axis or if it folds back, substituents even further away will as well. If the chain folds into the groove, the interactions within the HELOL ligand can be extended considerably. Figure 5 suggests that in the case of **1** when $n = 7$, the benzene ring at the penultimate carbon in the conformation of lowest energy lies within the helicene cleft in both diastereomers, oriented with an edge perpendicular to the terminal aromatic ring and near to that ring and to the phosphorus. The pictured model appears reasonable because benzene rings commonly adopt edge-to-face orientations.[27,28,29] Figure 5 also implies that the terminal methyl group of the alkoxy chain points away from the helicene structure not

(16) Measured by the weights of the (*R*) and (*S*) materials that were combined. The analyses of the (*R*) and (*S*) materials show that any slight deviation from their enantiopurity cannot significantly change the calculated ee.

(17) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

(18) (a) AMBER: Cornell, W. D.; Cieplak, P.; Bayly, C. I.; Gould, I. R.; Merz, K. M., Jr.; Ferguson, D. M.; Spellmeyer, D. C.; Fox, T.; Caldwell, J. W.; Kollman, P. A. *J. Am. Chem. Soc.* **1995**, *117*, 5179. (b) AMBER* is a variation used in the Macromodel program, ref 17.

(19) When the solvent was water, there were only two conformers within 4 kcal/mol of the global minimum, but when $CHCl_3$, there were five within 2 kcal/mol of the global minimum and eight total within 3 kcal/mol.

(20) The reagent used for $Et(Me)CH(CH_2)_3OH$ was α-cyano-α-fluorophenylacetic acid.[4]

(21) Reagents **2a** (in this experiment, NMe_2 took the place of the pictured Cl) and **2b** are reported not to distinguish the enantiomers of 4-methylhexanol.[3a,5] They do distinguish those of 2-methylbutanol, as does **3**[3b] and a related reagent (Wu, R.; Odom, J. D.; Dunlap, R. B.; Silks, L. A., III *Tetrahedron: Asymmetry* **1999**, *10*, 1465).

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(23) Chromatography on a chiral column was used to resolve lipoic acid.[24] A binaphthyl column was used to separate the 3,5-dinitroanilides of the 4-phenylvaleric acids.[25]

(24) Fadnavis, N. W.; Koteshwar, K. *Tetrahedron: Asymmetry* **1997**, *8*, 337.

(25) Oi, S.; Ono, H.; Tanaka, H.; Matsuzaka, Y.; Miyano, S. *J. Chromatogr. A* **1994**, *659*, 75.

(26) (a) Pirkle, W. H.; Pochapsky, T. C. *Chem. Rev.* **1989**, *89*, 347. (b) Pirkle, W. H.; House, D. W. *J. Org. Chem.* **1979**, *44*, 1957. (c) Taylor, D. R.; Maher, K. *J. Chromatogr. Sci.* **1992**, *30*, 67.

(27) Hunter, C. A. *Chem. Soc. Rev.* **1994**, *23*, 101.

(28) (a) Müller-Dethlefs, K.; Hobza, P. *Chem. Rev.* **2000**, *100*, 143 and references therein. (b) Boyd, D. R.; Evans, T. A.; Jennings, W. B.; Malone, J. F.; O'Sullivan, W.; Smith, A. *J. Chem. Soc., Chem. Commun*. **1996**, 2269 and references therein.

(29) The reasons are unclear (see: Kim, E.-I.; Paliwal, S.; Wilcox, C. S. *J. Am. Chem. Soc*. **1998**, *120*, 11192, references therein, and refs 27 and 28a), and molecular mechanics calculations do not account for them.[27]

just in one of the diastereomers, but in both, and that the chain folds to accommodate this requirement. The consequence is a change in the orientation of the chain that, in turn, can alter the angles at the phosphorus nucleus and therefore the phosphorus chemical shift. Most importantly, Figure 5 shows that the alkoxy group of **1** with $n = 7$ does fit into **5**'s cleft.

In line with these thoughts, the effect that the change in solvent from $CDCl_3$ to CD_3CN exerts on the ^{31}P chemical shifts of the diastereomers **5** [X = $O(CH_2)_{6-7}CHMePh$] might be a consequence of the latter, more polar solvent favoring more compact conformations for these molecules—that is, those in which the alkyl chains lie within the cleft.[30] The calculations described above addressing this hypothesis indicate that when the solvent is chloroform, while the lowest energy conformations are similar to the ones in Figure 5, there are a few just slightly higher in energy in which the chains are extended. When the solvent is water, no such extended conformations are found to have energies near that of the global minimum. However, when an attempt was made to extend the analyses of alcohols $HO(CH_2)_nCHMeEt$ to $n = 5$ by changing the solvent from $CDCl_3$ to CD_3CN, only a single resonance was observed in the latter solvent, and only a slightly split resonance in the former. While it is unfortunate that the enantiomers of 6-methyloctanol could not be analyzed, it would have been remarkable if the small differences among an H, Me, and Et so remote from their point of attachment to a reagent could be distinguished.

We have been unable to find data to compare the effects that changes in solvents have on the ^{31}P NMR chemical shifts of other phosphite esters. However, in analyzing enantiomers by derivatizing them with molecules similar to **3**, Silks et al. studied the effects solvents had on the ^{77}Se chemical shifts of the resulting selenones. They found that when the solvent's polarity increases, the shielding of the selenium nuclei increases and the difference between the chemical shifts of the diastereomers decreases. The data for the ^{31}P resonances of the alcohol derivatives studied here are exactly opposite. In the more polar solvent (acetonitrile), the shielding of the ^{31}P nuclei decreases, and the difference between the chemical shifts of the diastereomers increases (Figures 1 and 2). In the case of the derivatives of the carboxylic acids (Table 4), the switch from $CDCl_3$ to CD_3CN *decreases* $\Delta\delta$ when $n = 4$, but increases it when $n = 5$. In addition, the line widths became narrower in both cases (the peak width at half-height when $n = 4$ was 4.0 Hz; when $n = 5$, it was 4.8 Hz). This last effect might be a consequence of the viscosities decreasing.[31] However, in the case when $n = 4$, contrary to these expectations, the lines were broader when the solvent was Et_2O, which is less viscous than CD_3CN and $CDCl_3$.[31] Also in this case $\Delta\delta$ was larger, even though the polarity was lower.

Finally we note that Kolodiazhyni and co-workers have reported a chiral derivatizing agent related to **5**, dimenthyl chlorophosphite, and showed how it can be used to analyze protected amino acids.[32] However, in a direct comparison with **5**, we found that while dimenthyl chlorophosphite can distinguish the enantiomers of 3-phenylbutanol, it cannot distinguish the enantiomers of 4-phenylpentanol and can only partially distinguish those of 3-methylpentanol. (The resolution is not to the baseline.[33]) In contrast, **5** (X = Cl) distinguishes the enantiomers of all of them. The difference is likely a consequence of the greater depth of [5]HELOL's cleft.

Conclusions

The chlorophosphite of [5]HELOL is by far the most sensitive probe of remote chirality. Its preparation is easy, the analyses are fast, and the reagent can be applied to a variety of materials: alcohols, amines, and carboxylic acids. For these last, 2-aminophenol proved to be an effective linker that allowed chiral centers remote from the acid function to be analyzed. The experiments show that solvent effects can be used to extend the range of the analyses.

Experimental Section

THF was distilled from sodium-benzophenone ketyl, CH_2Cl_2 and Et_3N from CaH_2. $CDCl_3$ was stored over 4 Å molecular sieves, and just before it was used, it was filtered through basic alumina. PCl_3 was used as a 0.115 M solution in CH_2Cl_2. All materials were purchased from Aldrich except for the basic alumina (Acros) and, unless noted, were used without further purification. ^1H NMR spectra were recorded at either 300 or 400 MHz (TMS standard) and ^{13}C NMR spectra at 75 MHz ($CDCl_3$ standard). The usual procedure for determining ^{31}P NMR spectra was to record them at 121.5 MHz with continuous proton decoupling. After 30° pulses (2.5 μs), the FIDs were acquired for 0.675 s. The sweep width was 200 ppm, centered at 80 ppm, and referenced to zero for the resonance of 85% w/w H_3PO_4 in a sealed capillary tube. The relaxation delay was 0.8 s. Zero-filling by a factor of at least 2 was applied before the Fourier transformation. No window function was applied. The results were not noticeably different when inverse-gated or no proton decoupling was applied or the relaxation delay was extended. For the experiments in Figure 1, the acquisition time was increased slightly, to 0.8 s.

Preparation of (*M, M*)-(−)-[5]HELOL. (*M,M*)-(−)-[5]HELOL (**6**) was prepared following the published procedure.[34] The enantiomeric purity of its [5]helicene precursor was high. (*M,M*)-(−)-[5]HELOL (**6**) was shown to be ≥98% enantiopure as follows. The de's, according to ^{31}P NMR analyses (Figures 4a and 4b) of the derivatives **5** (X = $O(CH)_2CHMe(CH_2)_2CH{=}CMe_2$) formed by combining **5** (X = Cl, prepared from **6** and PCl_3 as described below) and (*S*)−(−)-*β*-citronellol and (*R*)−(+)-*β*-citronellol, are >98%.

5 (X = (*S*)-(−)-*β*-citronelloxy) ^{31}P NMR: 129.2 ppm (*S*:*R* > 107:1). **5** (X = (*R*)−(+)-*β*-citronelloxy) ^{31}P NMR: 128.8 ppm (*S*:*R* > 103:1).

Preparation of Reagent 5 (X = Cl) and Its Conversion into 5 (X = OR* or NHR*). PCl_3 (0.025 mmol as its solution in CH_2Cl_2), followed immediately by Et_3N (21 μL, 0.151 mmol), was added by syringe to 20 mg (0.028 mmol) of **6** and a very small amount of DMAP, contained along with a stir bar in a 1 dram vial that had been evacuated and filled with N_2. The resulting brownish yellow solution was stirred for 10 min at 25 °C, and then the alcohol or amine (as a solution in CH_2Cl_2 if it was a solid) was syringed in. The mixture was stirred for 2 h to allow the alcohol or amine time to react completely. The resulting greenish solution, diluted with $CDCl_3$, was pipetted into an NMR tube, and the ^{31}P spectrum was recorded.

If the peaks were insufficiently resolved, the solvent was changed. Since decomposition seemed to occur if the solvent was evaporated at this point, the solution was chromatographed on a short plug of silica gel, which removes very polar impurities ($Et_3N{\cdot}HCl$). The eluting solvents were varying mixtures of CH_2Cl_2−hexanes or EtOAc−hexanes

(30) For changes in the conformations of aromatic molecules that occur when the solvent is changed from chloroform to acetonitrile, see: Prince, R. B.; Saven, J. G.; Wolynes, P. G.; Moore, J. S. *J. Am. Chem. Soc.* **1999**, *121*, 3114 and references therein.

(31) The viscosities of ether (0.224 P at 25 °C) and acetonitrile (0.369) are both lower than that of chloroform (0.537) (*CRC Handbook of Chemistry and Physics*, 73rd ed.; Lide, D. R., Ed.; CRC: Ann Arbor, MI, 1992).

(32) Kolodiazhnyi, O. I.; Demchuk, O. M.; Gerschkovich, A. A. *Tetrahedron: Asymmetry* **1999**, *10*, 1729. They also report that the chemical shift difference is even larger in the spectra of the corresponding oxide or sulfide (it is unclear which). Usually chemical shift differences are smaller in the derivatives of P(V) than in the corresponding ones of P(III). See: refs 2b and 3a.

(33) The spectra are displayed in the Supporting Information.

(34) While ref 7 states correctly on p 820 that 82 g of KOH was used to prepare the dehydro-derivative of **6**, it states incorrectly that this amount is 55 mmol. It is 1.46 mol. A salt-ice bath kept the temperature of the reaction mixtures at 0 ± 2 °C.

that were chosen on the basis of TLC analyses. The column can be very short because impurities such as **6** (yellow, as is **5**) and **6**'s oxidation product (dark blue) need not be separated. The solvent could then be evaporated and replaced. If necessary, the evaporation of solvent and its replacement could then be repeated.

The ^{31}P NMR chemical shifts (in ppm) of the products were as follows. Table 1, $n = 0$, R = Ph: 143.18, 142.44; Table 1, $n = 1$, R = Ph: 128.51, 127.14; Table 1, $n = 2$, R = Ph: 131.51, 131.20; Table 1, $n = 3$, R = Ph: 128.01, 127.80; Table 1, $n = 4$, R = Ph: 128.76, 128.45; Table 1, $n = 5$, R = Ph: 129.40, 129.13; Table 1, $n = 6$, R = Ph, $CDCl_3$: 129.16, 129.14, CD_3CN: 135.40, 135.25; Table 1, $n = 7$, R = Ph, $CDCl_3$: 129.18, 129.16, CD_3CN: 135.24, 135.17; Table 1, $n = 8$, R = Ph, $CDCl_3$: 128.75, 128.74, CD_3CN: 135.36; Table 1, $n = 1$, R = Et: 132.19, 132.11; Table 1, $n = 2$, R = Et: 131.69, 131.25; Table 1, $n = 3$, R = Et: 128.98, 128.79; Table 1, $n = 4$, R = Et: 129.04, 129.00; Table 1, $n = 5$, R = Et: 129.20; Table 2, entry 1: 150.44, 149.68; Table 2, entry 2: 150.26, 149.96; Table 2, entry 3: 149.21, 148.41; Table 2, entry 4: 143.20, 142.82; Table 2, entry 5: 148.48, 146.03; Table 2, entry 6: 145.04, 144.13; Table 3, entry 1: 146.07, 143.78; Table 3, entry 2: 140.36, 137.15; Table 3, entry 3: 149.80, 141.75; Table 3, entry 4: 137.08, 136.67; Table 3, entry 5: 137.53, 137.32; Table 3, entry 6: 129.15, 128.83; Table 4, $n = 1$, R = Ph: 134.06, 133.10; Table 4, $n = 2$, R = Ph: 132.33, 130.50; Table 4, $n = 3$, R = Ph: 132.87, 132.45; Table 4, $n = 4$, R = Ph, $CDCl_3$: 132.63, 132.45, diethyl ether (with a small amount of $CDCl_3$ to provide a lock signal): 134.23, 133.97, CD_3CN: 131.54, 131.43; Table 4, $n = 5$, R = Ph, $CDCl_3$: 133.00, 132.93, CD_3CN: 133.32, 133.16; Table 4, $n = 6$, R = Ph, $CDCl_3$: 133.21, CD_3CN: 133.08, 133.06.

Preparation of 5 (X = $OCH_2CHEtMe$). **5** was prepared as described above except that all quantities were doubled. The product was chromatographed (flash chromatography, eluting with 1:1 CH_2Cl_2−hexanes), yielding 27.0 mg (87% yield) of a bright yellow powder. ^{1}H NMR (300 MHz, $CDCl_3$): 8.30−8.26 (m, 2H), 7.97−7.78 (series of m, 4H), 7.70−7.51 (series of m, 8H), 7.26 (d, 6.4 Hz, 2H), 7.19−7.07 (m, 2H), 6.91−6.86 (m, 2H), 4.26 (d, 5.0 Hz, 6H), 4.17 (s, 6H), 1.53 (s, 0.5 H), 1.41−1.33 (m, 1H), 1.28−1.26 (m, 1H), 1.19−1.12 (m, 0.5H), 0.45−0.15 (series of m, 5H), 0.09−0.00 (m and d under the TMS resonance, 2H), −0.15 (d, 6.5 Hz, 1H) ppm. ^{31}P NMR (122 MHz, external 85% w/w H_3PO_4 standard): 132.0 and 131.9 ppm. IR (CCl_4): 1213, 1164, 906, 835, 789, 738, 731 cm^{-1}. HRMS (FAB, M + 1): *m*/*z* calcd for $C_{53}H_{43}O_7P$ 822.2746, found 822.2750.

Condensation of Acids with 2-Aminophenol. The acid (1 mol) was stirred under N_2 for 30 min with oxalyl chloride (11 mmol). The excess oxalyl chloride was removed in vacuo, and the residue, dissolved in CH_2Cl_2 (3.3 mL), was added by cannula to a solution, cooled to 0 °C, of 2-aminophenol (1.5 mmol) and pyridine (37 mmol) in CH_2Cl_2 (8.6 mL). The mixture was stirred at 0 °C for 1 h and at 25 °C for 2 h. After 1 M HCl had been added, the product was extracted with EtOAc. The EtOAc solution was washed with brine and dried (Na_2SO_4). Removal of the solvent left a brown viscous oil or wax, which after flash chromatography, eluting with 50−60% EtOAc−50−40% hexanes, yielded a yellow-orange oil whose ^{1}H NMR and ^{13}C NMR showed only the expected resonances.

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Supporting Information Available: Preparations of alcohols and acids that could not be purchased, ^{31}P NMR spectra of all alcohols, amines, and acids analyzed and of the dimenthyl chlorophosphite derivatives discussed in the text (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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