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A [5]HELOL Analogue That Senses Remote Chirality in Alcohols, Phenols, Amines, and Carboxylic Acids

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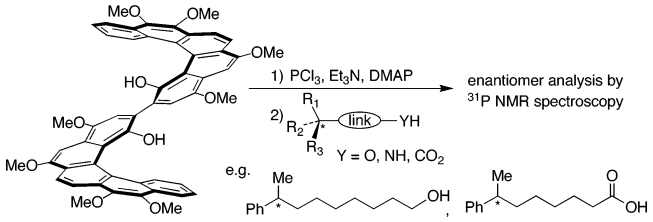
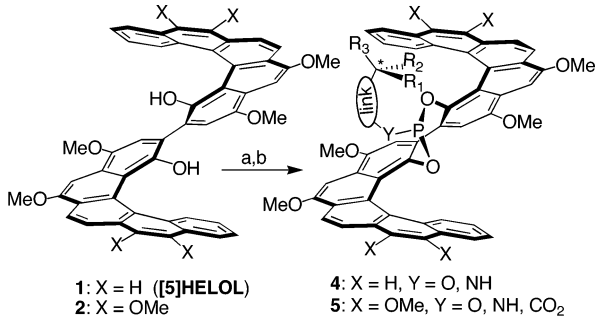


A route is developed to a structural analogue of [5]HELOL, a previously reported helically grooved sensor of remote chirality. It gives the material enantiomerically pure and in multigram quantities. The enantiomers of alcohols, phenols, amines, and carboxylic acids, even when their centers of chirality are remote from any functional groups, can be differentiated by ^{31}P NMR spectroscopic analyses of their reaction products with the chlorophosphite of this material.

Introduction

An earlier publication reported that a helically grooved sensor of remote chirality, the chlorophosphite of a bis-[5]helicenediol **1**, called [5]HELOL, can be used to distinguish the enantiomers of a variety of alcohols, phenols, amines, and, after they had been coupled to 2-aminophenol, carboxylic acids.[1,2] As summarized in Scheme 1, this was done by combining [5]HELOL in CH_2Cl_2 with PCl_3, Et_3N, and DMAP and then with the material to be analyzed [$R_1R_2R_3C$*-link-YH (Y = O, NH)], referred to below as **3**. The resulting derivatives, **4**, were then analyzed by ^{31}P NMR spectroscopy. Notable was the ability of the reagent,[3] like others devised recently,[4,5] to distinguish configurations of stereogenic centers remote from a functional group. Chromatographic[6] and other methods[7] for such analyses have also been developed, but most of these, like the NMR spectroscopic methods, work only with restricted structures (only alcohols,[5a−c,6b,c] or

SCHEME 1[a]



[a] Reagents and conditions: (a) PCl_3, DMAP, Et_3N, CH_2Cl_2, 25 °C, 15 min; (b) analyte **3** [$R_1R_2R_3C$*-link-YH (Y = O, NH, CO_2)], 25 °C, 2 h.

(1) Weix, D. J.; Dreher, S. D.; Katz, T. J. *J. Am. Chem. Soc.* **2000**, *122*, 10027.

(2) Dreher, S. D.; Katz, T. J.; Lam, K.-C.; Rheingold, A. L. *J. Org. Chem.* **2000**, *65*, 815.

(3) The ability of the HELOL to distinguish configurations of remote stereogenic centers was attributed to the substrate moiety positioning itself within the helical groove of **4**; therefore, even though many bonds separate them, a stereogenic center (for example that in racemic 8-phenylnonanol) and the HELOL structure to which it is bound remain close together. The evidence was the observation in a few examples that the effects of remote stereogenic centers on phosphorus chemical shifts were larger when the solvent was the more polar acetonitrile, rather than chloroform, and the implication of a calculation that showed conformations in which hydrocarbon links were positioned within the helical groove to be favored by polar solvents.

(4) See footnotes 2−5 in ref 1.

(5) For alcohols: (a) Wu, R.; Odom, J. D.; Dunlap, R. B.; Silks, L. A., III. *Tetrahedron: Asymmetry* **1995**, *6*, 833, and references therein. (b) Alexakis, Y.; Mutti, S.; Mangeney, P. *J. Org. Chem.* **1992**, *57*, 1224. (c) Gras, J.-L.; Soto, T.; Heumann, A. *Eur. J. Org. Chem.* **2000**, 837. For alcohols and amines: (d) Takeuchi, Y.; Itoh, N.; Note, H.; Koizumi, T.; Yamaguchi, K. *J. Am. Chem. Soc.* **1991**, *113*, 6318. (e) Takeuchi, Y.; Itoh, N.; Satoh, T.; Koizumi, T.; Yamaguchi, K. *J. Org. Chem.* **1993**, *58*, 1812. For carboxylic acids: (f) Silks, L. A., III; Dunlap, R. B.; Odom, J. D. *J. Am. Chem. Soc.* **1990**, *112*, 4979. (g) Peng, J.; Barr, M. E.; Ashburn, D. A.; Lebioda, L.; Garber, A. R.; Martinez, R. A.; Odom, J. D.; Dunlap, R. B.; Silks, L. A., III. *J. Org. Chem.* **1995**, *60*, 5540. (h) Silks, L. A., III; Peng, J.; Odom, J. D.; Dunlap, R. B. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2495. (i) Yang, D.; Li, X.; Fan, Y.-F.; Zhang, D.-W. *J. Am. Chem. Soc.* **2005**, *127*, 7996. (j) Hedenström, E.; Nguyen, B.-V.; Silks, L. A., III. *Tetrahedron: Asymmetry* **2002**, *13*, 835.

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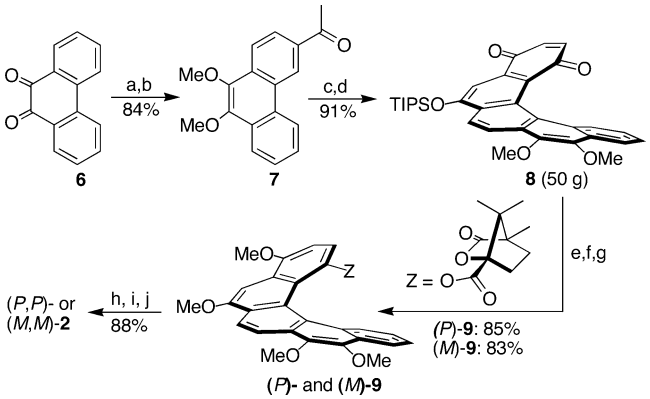
alcohols and amines,[5d,e] or only carboxylic acids[5f–j,6d]), and they fail when a stereocenter and the nearest functional group are too far apart, usually three or more bonds.[5,6] An extraordinary exception is one developed by Ohrui, which has allowed HPLC to distinguish enantiomers whose only stereocenters were 23 bonds removed from a carboxyl group.[6d] Advantages of the [5]HELOL reagent are then both its sensitivity to remote chirality and its applicability to a variety of substrates: alcohols, phenols, amines, and carboxylic acids.[1]

However, the use of the reagent also has deficiencies, and in this report we address some of them. One is that the 3-acetylphenanthrene from which [5]HELOL is synthesized[2] is always accompanied by appreciable amounts of 2-acetylphenanthrene.[8] In the previous study a procedure was developed to overcome the contamination,[2] but it requires an extra step in the synthesis. Additionally, the procedure diverts some of the material to an unwanted product, and requires the inconvenience of a purification step carried out in the absence of light. A second deficiency of the original procedure relates to the carboxylic acids. These were analyzed as their 2-hydroxyanilide derivatives which, while effective, required that the procedure include an extra step for the derivatization. We, therefore, describe here the synthesis of a more readily available analogue of [5]HELOL, structure **2**, and show how it can be applied to analyze the enantiomeric compositions of a variety of chiral materials. Carboxylic acids, it is shown, can be analyzed directly, without prior derivatization.

Results and Discussion

The synthesis of **2** starts from phenanthrenequinone, **6**, which is readily available, and proceeds, as shown in Scheme 2, through three intermediates. Reduction with $Na_2S_2O_4$ and methylation with Me_2SO_4 transforms **6** into 9,10-dimethoxyphenanthrene,[9] which, on acylation with 1 equiv of $AlCl_3$, gives **7** in 84% yield. The latter step was developed as a corrolary of an observation made earlier, that Friedel–Crafts acetylation could be used to introduce acetyl groups specifically into both the 3- and the 6-positions of 9,10-dialkoxyphenanthrenes.[9] What was found now is that when 1 equiv of acetyl chloride is used, no diacetylated product is obtained. Only **7** is obtained.

SCHEME 2[a]



[a] Reagents and conditions: (a) $Na_2S_2O_4$, KOH, Bu_4NBr, Me_2SO_4, H_2O/THF (1:1), 25 °C, 20 min; (b) $AlCl_3$, AcCl, CH_2Cl_2, −20 to 25 °C, 3 h; (c) triisopropylsilyl triflate, Et_3N, CH_2Cl_2, 0 °C, 30 min, then 25 °C, 2 h; (d) *p*-benzoquinone, toluene, reflux, 24 h; (e) $Na_2S_2O_4$, EtOAc/H_2O/CH_2Cl_2 (2:3:1), 25 °C, 40 min; (f) HCl-saturated MeOH, $ClCH_2CH_2Cl$, 60 °C, 2 h; (g) (1*S*)-(−)-camphanoyl chloride, DMAP, Et_3N, $ClCH_2CH_2Cl$, 100 °C, 1.5 h; (h) KOH, EtOH, 0 °C, 2 h; (i) Ag_2O, Et_3N, CH_2Cl_2, 0 °C, 2 h; (j) Zn, AcOH, acetone, 0 °C, 2 h.

[5]Helicenequinone **8** is then formed in 91% yield by combining **7** with triisopropylsilyltriflate (TIPSOTf) and triethylamine (which gives the TIPS-enol ether) and then excess *p*-benzoquinone.[10] In this way 50 g of **8** was easily prepared. A Russig–Laatsch reaction[11] then converts the quinone moiety of **8** into the hydroquinone monomethyl ether while at the same time it replaces the OTIPS group by a methoxyl group. The significant discovery is that, in contrast to the corresponding step in the synthesis of [5]HELOL,[2] the procedure gives no recognizable amount of a benzoperylene byproduct even when the reaction is run for a long time (ca. 4 h at 60 °C) and in the presence of light. Thus, the product of this step is clean enough to be used for the next step without purification. Refluxing a solution of the resolving reagent, (1*S*)-(−)-camphanoyl chloride, Et_3N, and a catalytic amount of DMAP in 1,2-dichloroethane at 100 °C for 1.5 h gives the diastereomeric camphanates, (*P*)- and (*M*)-**9**. The yield from the three steps is 84%.

(*P*)- and (*M*)-**9** were easily separated on a scale of ca. 20 g by a combination of trituration with ether [to isolate the less-soluble isomer, which as expected[2,12] is the (+)- and presumably[2,12,13] (*P*)-isomer] and chromatography on a silica gel plug, eluting with hexane–CH_2Cl_2 [to isolate the (−)- and presumably (*M*)-isomer]. The stereochemical purities of the materials were analyzed by integrating the intensities of the ^{1}H NMRs of the camphanate methyl singlets, at δ 0.38 ppm in (*P*)-**9** and 0.65 ppm in (*M*)-**9**. The diastereomeric excesses for both isomers were >98%. As expected, because the camphanate esters are at the 1-positions of the [5]helicene skeletons,[2,14] both (*P*)- and (*M*)-**9** are stable to racemization under the conditions of

(6) (a) See footnote 1 in ref 1. For HPLC methods for alcohols: (b) Ohtaki, T.; Akasaka, K.; Kabuto, C.; Ohrui, H. *Chirality* **2005**, *17*, S171, and references therein. (c) Oi, S.; Ono, H.; Tanaka, H.; Shijo, M.; Miyano, S. *J. Chromatogr. A* **1994**, *679*, 35. For HPLC methods for carboxylic acids: (d) Akasaka, K.; Ohrui, H. *Biosci. Biotechnol. Biochem.* **2004**, *68*, 153, and references therein.

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(11) (a) Russig, F. *J. Prakt. Chem.* **1900**, 33. (b) Laatsch, H. *Liebigs Ann. Chem.* **1980**, 140. (c) Dreher, S. D.; Paruch, K.; Katz, T. J. *J. Org. Chem.* **2000**, *65*, 806.

(12) Thongpanchang, T.; Paruch, K.; Katz, T. J.; Rheingold, A. L.; Lam, K.-C.; Liable-Sands, L. *J. Org. Chem.* **2000**, *65*, 1850.

their preparation. There is no sign that any appreciable change occurs during eight months of storage at room temperature in the air.

A three-step procedure—saponification, Ag_2O oxidation, zinc dust reduction—analogous to that used to prepare **1**, then converts (*P*)- **9** into (*P*,*P*)-**2** and (*M*)-**9** into (*M*,*M*)-**2**. The yields are 88%. We note that, as discussed previously,[2] the configuration of the biaryl moiety in (*P*,*P*)-**2** must be (*S*) and in (*M*,*M*)-**2** (*R*). Although the isolation of **2** at the end of this sequence involves neither chromatography nor recrystallization,[15] ^{1}H NMR analyses implied that the products were contaminated with <5% of other materials, structural purities sufficient for the analyses described below.

The enantiomeric purities of (*P*,*P*)-**2** and (*M*,*M*)-**2**, presented as enantiomeric excess (ee), were >98%. The analyses were carried out by measuring the intensities of the ^{31}P NMRs of the diastereomers formed when (*P*,*P*)- or (*M*,*M*)-**2** was combined with PCl_3 and then with 1-phenylethylamine, **10a**, whose ee was ≥99.0%.[16] Analyses of (*M*,*M*)-**2** are illustrative. The ^{31}P NMRs of the phosphonamides **5** formed when (*M*,*M*)-**2** is combined with (*S*)- or (*R*)-**10a** are comprised of singlets at 151.09 and 150.86 ppm, respectively, relative to external 85% H_3PO_4, the region of the spectrum where phosphite resonances typically appear.[17] When (*M*,*M*)-**2** was combined with (±)-**10a**, both of these singlets were seen, and the ratio of their intensities was 0.998 ± 0.02.[18] When it was combined with a sample of **10a** prepared (by combining weighed amounts of the (*R*)- and (*S*)-materials) to have an ee of 50.1 ± 0.1%, enriched in the (*R*)-enantiomer, the ratio of the intensities was 3.008 ± 0.07,[18] corresponding to an ee of 50.1 ± 0.8%. The stability of **2** is similar to that of [5]HELOL **1**.[1] According to analyses such as the one described above, neither the solid after storage either at 4 °C or at room temperature under nitrogen for one month, nor a solution in CH_2Cl_2 after storage at room temperature for 3 days, loses any detectable enantiopurity. However, like **1**, **2** is oxidized by air to the corresponding 2,2′-diphenoquinone. This occurs slowly when **2** is solid, but when **2** is dissolved in CH_2Cl_2, $CDCl_3$, or MeCN, a change in color from light yellow to blue-green shows its occurrence in the course of hours. The practical implication is that **2** either be stored as a solid under nitrogen at 4 °C or (because it is easy to do) be prepared as required from (*P*)- or (*M*)-**9**.

The procedure used to analyze the enantiomeric purities of (*P,P*)-**2** and (*M,M*)-**2** could, in turn, be applied with these helicenes to analyze the enantiomeric purities of amines, alcohols (and phenols), and carboxylic acids. Scheme 3 summarizes the results of numerous experiments in which racemic materials[19] were combined with the chlorophosphites of (*P,P*)- or (*M,M*)-**2**. Below each structure, the scheme shows $\Delta\delta$, the difference between the ^{31}P NMR chemical shifts of the diastereomers of **5** in $CDCl_3$ or CD_3CN. Notable is that baseline resolution was achieved in every case except that of **12e**. Also worth noting is that the use of a stock solution of enantiopure **2** and Et_3N in CH_2Cl_2 allowed the analyses to be achieved rapidly. In all cases[19] the ratios of the two phosphorus resonance intensities were found, within experimental error,[18] to be 1:1. Moreover, in every case but one, this was the measured ratio even when 20% less of reagent **2** than was stoichiometrically required was combined with the analyte. That is, the analyses were usually not biased by kinetic resolutions. The one exception noted was that of **10e**. The ratio of the intensities of the phosphorus resonances was (as required) 1.01 when the molar ratio of **2** and **10e** was 1.2/1, but it was 1.26 when the ratio was 1/1.2.

Some nonracemic mixtures of known composition were also analyzed. A sample of 12.6 ± 0.1% ee **11l**, prepared by combining 56.3 weighed parts of the (*R*)-enantiomer and 43.7 of the (*S*) (the ee of each enantiomer was >98%),[16] was measured to have an ee of 12.9 ± 1%. A sample of 31.9 ± 0.4% ee **11p**, prepared by combining 33.5 weighed parts of (1*R*,2*S*)-**11p** (99% ee)[16] and 66.5 parts of (1*S*,2*R*)-**11p** (98% ee),[16] was measured to have an ee of 33.6 ± 0.9%. Also, in the case of a molecule with two chiral centers, **11r**, four phosphorus resonances were measured when the sample in CD_3CN was analyzed, allowing the analysis of both the diastereomeric (16.4%) and enantiomeric excesses (2.7% and 3.7%).

As in the earlier study using [5]HELOL,[1] the solvent affects the resolution achieved, and for most of the alcohols analyzed, the resolution was greater when the solvent was CD_3CN than when it was $CDCl_3$. The reverse was true for three of the alcohols (**11d**, **k**, and **p**) and two of the carboxylic acids (**12c** and **h**). Whatever the theoretical bases, the practical point is that, with the exception of **12e**, baseline resolution could be achieved in one of the two solvents for every molecule in the scheme.

The mixed anhydrides formed from carboxylic acids rearrange slowly (in ca. 2−4 h) to α-ketophosphonates [$(RO)_2POC(O)R' \rightarrow (RO)_2P(O)C(O)R'$][20] as evidenced by decreases in the intensities of the ^{31}P resonances at low fields (ca. δ 130−140 ppm), the region of the NMR

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(15) Purification by means of column chromatography was investigated, but it requires protection from the atmosphere, results in a 10−20% loss in yields, and does not improve the enantiomer analyses.

(16) GLC analysis, according to the supplier, Aldrich Chemical Co.

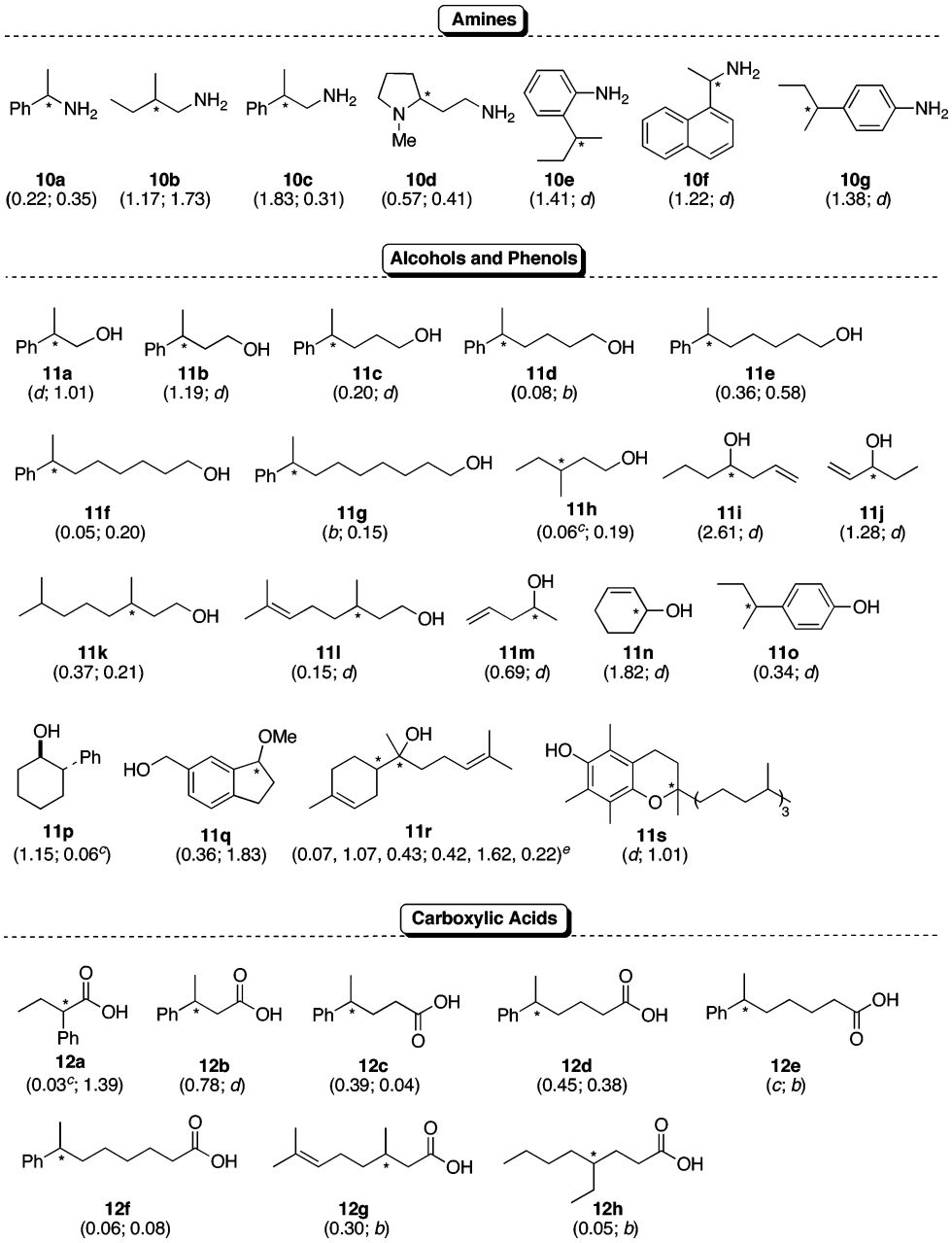
(17) For examples, see: (a) Wang, L.; Li, Y.-M.; Yip, C.-W.; Qiu, L.; Zhou, Z.; Chan, A. S. C. *Adv. Synth. Catal.* **2004**, *346*, 947. (b) Reetz, M. T.; Mehler, G.; Meiswinkel, A.; Sell, T. *Tetrahedron: Asymmetry* **2004**, *15*, 2165. (c) Huang, H.; Liu, X.; Chen, H.; Zheng, Z. *Tetrahedron: Asymmetry* **2005**, *16*, 693.

(18) According to the spectra displayed in the Supporting Information, the average relative error in the analyses of 40 racemates is 2.2%. For a comprehensive treatment of quantitative analyses by NMR spectroscopy, see: Pauli, G. F.; Jaki, B. U.; Lankin, D. C. *J. Nat. Prod.* **2005**, *68*, 133.

(19) Compound **11p** was analyzed only as an enantiomerically enriched mixture. See the text.

(20) (a) Livantsov, M. V.; Proskurnina, M. V.; Prishchenko, A. A.; Lutsenko, I. F. *J. Gen. Chem. USSR* **1984**, *54*, 2237. (b) Pudovik, A. N.; Gazizov, T. Kh.; Pashinkin, A. P. *J. Gen. Chem. USSR* **1966**, *36*, 583. (c) Al′fonsov, V. A.; Girfanova, Yu. N.; Zamaletdinova, G. U.; Batyeva, E. S.; Pudovik, A. N. *Dokl. Chem.* **1980**, *251*, 99. (d) Kamil, W. A.; Bond, M. R.; Willett, R. D.; Shreeve, J. M. *Inorg. Chem.* **1987**, *26*, 2829.

SCHEME 3[a]



[a] The numbers in the parentheses are the differences between the ^{31}P NMR chemical shifts ($\Delta\delta$, in ppm) of the diastereomers **5**, first in $CDCl_3$ and second in CD_3CN. A star denotes chirality. [b]Unresolvable. [c]Not baseline resolved. [d]Not determined. [e]The three $\Delta\delta$s separating the diastereomers' four consecutive resonances.

spectrum in which phosphites resonate,[21] and concomitant appearances of resonances at ca. δ −10 to 0 ppm, the region of the spectrum in which α-ketophosphonates resonate.[22] The structures of the rearranged products, in the case of **12d**, were also evidenced by the appearance in the IR spectrum of characteristic P=O stretching absorptions[23] at 1283 cm^{-1} and C=O stretching absorptions[23] at 1762 cm^{-1} rather than at 1718 cm^{-1}, where they appear in the unrearranged structures.[21a] The ^{31}P NMRs of the diastereomers formed from the racemic acids were of equal intensity whether they were observed in the phosphite region (in **12a**, **c**, and **f**), in the phosphonate region (in **12b**, **h**), or in both (**12d**, **g**).[24]

There is little difference between the abilities of the two [5]HELOL reagents **1** and **2** to distinguish the enantiomers of alcohols $CH_3PhCH(CH_2)_nOH$ ($n = 1-7$).[25] When the solvent is $CDCl_3$, the resolution is appreciably greater with **2** when $n = 2$ and appreciably smaller when

(21) Acyl phosphites [$RC(O)OP(OR')_2$] resonate at about 130 to 140 ppm. Examples: (a) Korostylev, A.; Monsees, A.; Fischer, C.; Börner, A. *Tetrahedron: Asymmetry* **2004**, *15*, 1001. (b) Toru, K.; Norio, Y.; Eiichi, Y. *Chem. Pharm. Bull.* **1973**, *21*, 312. (c) Belyaev, A.; Zhang, X.; Augustyns, K.; Lambeir, A.-M.; De Meester, I.; Vedernikova, I.; Scharpé, S.; Haemers, A. *J. Med. Chem.* **1999**, *42*, 1041.

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(23) Ogata, Y.; Tomioka, H. *J. Org. Chem.* **1970**, *35*, 596.

(24) In $CDCl_3$ the $\Delta\delta$ values in the two regions are the following: 0.45 ppm (phosphite region) and 0.03 ppm (phosphonates region) for **12d**; and 0.30 and 0.30 ppm for **12g**.

$n = 4$, but usually, where the data are available, the resolution is slightly greater when the reagent is **2**.

Reagent **2** is one of few[5f,g] that allow the enantiomeric compositions of carboxylic acids with remote stereocenters to be analyzed. In particular, it distinguishes configurations in **12f**, which has a stereocenter six bonds away from the carboxyl group. The resolution is to the baseline both when the solvent is $CDCl_3$ and when it is CD_3CN. Similarly, in **12h** it distinguishes a methyl group and a methylene group five bonds away from the carboxyl group. For comparison, the record distance between a stereocenter and a carboxyl group that has allowed configurations to be distinguished was five bonds[5g,h,j] when the analyses were by means of the Silks−Dunlap−Odom reagent,[5f−h] which distinguishes enantiomers by means of ^{77}Se NMR spectroscopy, and 23 bonds[6d] when the analyses were by means of the Ohrui reagent in conjuntion with HPLC. It is helpful that the analyses that used **2** could be performed without the acids having to be further derivatized.

An observation that, at first, seems strange is that in the homologous series of carboxylic acids $CH_3CH(Ph)(CH_2)_nCO_2H$ where n varies from 1 to 5, although the spectra of the mixed anhydrides (both in $CDCl_3$ and in CD_3CN) distinguish the enantiomers of **12d** ($n = 3$) and **12f** ($n = 5$), they fail to distinguish the enantiomers of **12e** ($n = 4$). They fail also when the solvent is C_6D_6 or diethyl ether mixed with a small amount of $CDCl_3$ (to provide a frequency-lock signal). A similar effect is observed (see Scheme 3) in the homologous series of alcohols $CH_3CH(Ph)(CH_2)_nOH$ (**11a**−**f**), the resolution of the phosphorus resonances of the diastereomers being greater when $n = 5$ than when $n = 4$. If the conformation of the chain is like that shown in Figure 5 of ref 1, with the chain protruding from the phosphorus atom and then winding back into the helicene cleft, a stereocenter six or seven atoms away from the phosphorus might interact least with the helicene skeleton.

In summary, enantiopure [5]HELOL analogue **2** is easy to prepare in significant quantities, and by means of its chlorophosphite the enantiomeric compositions can be analyzed of a variety of alcohols, phenols, amines, and carboxylic acids, including those whose chiral centers are remote from functional groups. The enantio-differentiating ability is comparable to, and in several cases superior to, that of [5]HELOL. To analyze many samples is easy and fast.

Experimental Section

3-Acetyl-9,10-Dimethoxyphenanthrene, 7. $AlCl_3$ (16.8 g, 0.126 mmol) was added to a solution in CH_2Cl_2 (350 mL) at −20 °C of acetyl chloride (75 mL, 1.05 mol) and 9,10-dimethoxyphenanthrene, the latter synthesized as previously[9b] described from 9,10-phenanthrenequinone (**6**, 95% pure, 26.3 g, 0.126 mmol) and used as the unpurified oily product (25.0 g). The mixture was gradually warmed to 25 °C, stirred for 3 h, diluted with CH_2Cl_2 (350 mL), and then poured slowly onto crushed ice (800 mL) in a separatory funnel (2 L). Washing (saturated $NaHCO_3$, 800 mL, then brine, 800 mL), drying (Na_2SO_4), filtering through Celite, removal of solvents, and drying under a vacuum gave a foamy solid, which crystallized from hexane/EtOAc (2:1), giving the majority of the product as a light-yellow solid. Additional material was obtained from the concentrated mother liquor by means of silica gel chromatography (eluting with 2:1 hexane/EtOAc—the first band was the pure product). The total yield was 28.2 g (84% based on pure **6**). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.02 (s, 1H), 8.50 (dd, 1H, 6.8, 1.8 Hz), 8.14 (dd, 1H, 6.8, 2.4 Hz), 8.08 (d, 1H, 8.4 Hz), 7.95 (dd, 1H, 8.7, 1.2 Hz), 7.55−7.47 (m, 2H), 4.03 (s, 3H), 3.97 (s, 3H), 2.62 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 197.4, 145.7, 142.8, 133.4, 131.8, 128.8, 128.5, 127.4, 126.9, 126.0, 125.2, 123.2, 122.2, 122.0, 121.9, 60.5, 26.3 ppm. IR (KBr): 2955, 2917, 2848, 1672, 1614, 1511, 1469, 1360, 1325, 1281, 1241, 1171, 1112, 1087, 1069, 835, 764 cm^{-1}. Mp: 87−88 °C. HRMS (FAB, *m*-nitrobenzyl alcohol): *m/z* calcd for $C_{18}H_{16}O_3$ 280.1099, found 280.1093.

Helicenequinone, 8. Et_3N (44.3 mL, 0.318 mol) and TIPSOTf (31.5 mL, 0.117 mol) were added sequentially to a solution, cooled to 0 °C, of **7** (29.8 g, 0.106 mol) in CH_2Cl_2 (250 mL). The solution was stirred at 0 °C for 30 min, then at 25 °C for 2 h. Diluted with CH_2Cl_2 (150 mL), it was washed with saturated aqueous $NaHCO_3$ (3 × 450 mL) and dried (Na_2SO_4). Removal of solvents and drying for 2 h under a vacuum gave a light brown oil, which was mixed with *p*-benzoquinone (previously purified by slurrying in CH_2Cl_2 with twice its weight of basic alumina, filtering through Celite, and drying under vacuum,[9] 115 g, 1.06 mol) in toluene (400 mL), and refluxed for 24 h (oil bath temperature ca. 130 °C). It was then cooled to 60 °C and filtered through Celite, which was then washed with CH_2Cl_2 (300 mL). The filtrate was concentrated, and excess *p*-benzoquinone was sublimed, which gave crude **8** as a dark red glass. This was stirred vigorously with 300 mL of 5:1 MeOH/H_2O, and the major portion of the product, a dark red solid, was filtered. Additional product was obtained by chromatographing the concentrated filtrate on silica gel (eluting with 3:1 hexane/EtOAc). The combined yield was 52.4 g (91% for the two steps). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.40 (d, 1H, 8.0 Hz), 8.39 (s, 2H), 8.29 (d, 1H, 8.0 Hz), 7.59 (s, 1H), 7.52 (t, 1H, 7.2 Hz), 7.40 (t, 1H, 7.2 Hz), 6.93 (d, 1H, 10.4 Hz), 6.84 (d, 1H, 10.4 Hz), 4.19 (s, 3H), 4.12 (s, 3H), 1.57−1.50 (septet, 3H), 1.23−1.20 (d, 18H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 185.1, 185.0, 156.5, 145.7, 142.8, 139.9, 135.8, 132.7, 129.9, 129.7, 129.6, 128.4, 127.8, 127.6, 126.8, 125.9, 125.2, 125.1, 122.3, 121.7, 120.7, 108.0, 61.4, 61.1, 18.3, 13.2 ppm. IR (KBr): 3069, 2948, 2867, 1663, 1594, 1570, 1513, 1489, 1477, 1412, 1387, 1343, 1298, 1250, 1221, 1168, 1100, 1075, 1059, 998, 966, 921, 885, 832, 779, 731, 682 cm^{-1}. Mp: >280 °C (decomp). HRMS (FAB, *m*-nitrobenzyl alcohol): *m/z* calcd for $C_{33}H_{38}O_5Si$ [M + 2H] 542.2491, found 542.2477.

Helicene Monocamphanates, (*P*)- and (*M*)-9. $Na_2S_2O_4$ (101 g, 0.58 mol) in H_2O (900 mL) and a solution of **8** (25.0 g, 0.046 mol) in CH_2Cl_2 (300 mL) and EtOAc (600 mL) were shaken in a 5 L separatory funnel until a light yellow color was fully developed (ca. 40 min). After the organic layer had been concentrated and dried under a vacuum for 3 h, giving a yellow solid, 1,2-dichloroethane (240 mL) was added, followed by MeOH (600 mL), which had been saturated with dry HCl gas. The solution was stirred at 60 °C for 2 h, cooled to 25 °C, and slowly poured into saturated aqueous $NaHCO_3$ (2 L) and CH_2Cl_2 (1.2 L) [**CAUTION:** much CO_2 is formed!]. The CH_2Cl_2 layer was washed with H_2O (2 L), dried (Na_2SO_4), and filtered. Removal of solvents and drying under a vacuum yielded a bright yellow cotton-like solid. 1, 2-Dichloroethane (500 mL) was added, followed by (1*S*)-(−)-camphanoyl chloride (15.0 g, 0.069 mol), Et_3N (120 mL), and DMAP (2.82 g, 0.023 mol). The mixture was refluxed for 1.5 h, cooled to 25 °C, diluted with CH_2Cl_2 (800 mL), washed sequentially with 1 N HCl (1.5 L), H_2O (1.5 L), saturated $NaHCO_3$ (1.5 L), and H_2O (1.5 L), dried (Na_2SO_4), and filtered. Removal of solvents left a light brown-yellow solid, which was triturated with Et_2O (3 × 800 mL), giving (*P*)-(+)-**9**. The ether solutions were combined and concentrated, and upon silica gel chromatography (eluting with hexane/CH_2Cl_2, gradients from 4:6 to 2:8 and then CH_2Cl_2) gave the faster-moving (*M*)-(−)-**9** diastereomer as well as a small amount of the slower-moving (*P*)-(+)-**9** diastereomer. The yield of (*M*)-(−)-**9** was 11.4 g (83% over three steps) and

(25) The data for **1** are in Table 1 of ref 1.

of (*P*)-(+)-**9** was 11.6 g (85% over three steps). ^{1}H NMR analyses showed both to be >98% diastereomerically pure.

(*P*)-(+)-**9**. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.36 (d, 1H, 8.8 Hz), 8.28 (d, 1H, 8.8 Hz), 8.17 (d, 1H, 8.0 Hz), 8.06 (d, 1H, 8.0 Hz), 7.52 (s, 1H), 7.36 (t, 1H, 7.6 Hz), 7.08 (t, 1H, 7.2 Hz), 6.78 (d, 1H, 8.4 Hz), 6.69 (d, 1H, 8.4 Hz), 4.06 (s, 3H), 4.01 (s, 3H), 3.99 (s, 3H), 3.88 (s, 3H), 1.52−1.45 (m, 1H), 1.33−1.26 (m, 1H), 1.07−0.98 (m, 2H), 0.83 (s, 3H), 0.58 (s, 3H), 0.38 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.9, 165.0, 153.5, 152.2, 144.3, 142.7, 140.5, 129.7, 128.3, 127.7, 126.7, 125.9, 125.5, 124.5, 123.2, 121.5, 121.0, 120.9, 120.2, 116.1, 104.9, 96.6, 90.3, 61.1, 60.8, 55.8, 55.7, 54.2, 53.9, 28.7, 28.5, 16.5, 16.1, 9.4 ppm. IR (KBr): 2964, 2940, 2833, 1790, 1770, 1618, 1602, 1524, 1499, 1459, 1422, 1397, 1344, 1286, 1254, 1237, 1110, 1090, 1049, 1033, 1000, 779, 734 cm^{-1}. Mp: 167−168 °C. $[\alpha]_D$ +798° (*c* 0.0015, CH_2Cl_2). HRMS (FAB, *m*-nitrobenzyl alcohol): *m/z* calcd for $C_{36}H_{34}O_8$ 594.2254, found 594.2252.

(*M*)-(−)-**9**. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.57 (d, 1H, 8.8 Hz), 8.47 (d, 1H, 8.8 Hz), 8.43 (d, 1H, 8.4 Hz), 8.24 (d, 1H, 8.4 Hz), 7.77 (s, 1H), 7.69 (t, 1H, 8.0 Hz), 7.35 (dd, 1H, 7.6, 8.4 Hz), 7.05 (d, 1H, 8.4 Hz), 7.01 (d, 1H, 8.4 Hz), 4.29 (s, 3H), 4.28 (s, 3H), 4.24 (s, 3H), 4.20 (s, 3H), 1.69−1.63 (m, 1H), 1.55−1.42 (m, 2H), 1.14−1.06 (m, 1H), 1.04 (s, 3H), 0.82 (s, 3H), 0.65 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 177.2, 165.1, 153.6, 152.2, 144.7, 142.4, 140.8, 130.1, 128.1, 127.8, 126.7, 126.4, 125.5, 125.4, 125.3, 124.7, 123.3, 121.6, 121.2, 121.1, 120.2, 115.7, 61.1, 61.0, 56.0, 54.3, 54.1, 29.8, 29.0, 28.6, 16.5, 16.3, 9.6 ppm. IR (KBr): 2963, 2940, 2840, 1790, 1748, 1618, 1603, 1523, 1500, 1458, 1420, 1397, 1343, 1286, 1252, 1236, 1164, 1111, 1085, 1049, 1034, 1001, 765, 732 cm^{-1}. Mp: 169−170 °C. $[\alpha]_D$ −825° (*c* 0.0015, CH_2Cl_2). HRMS (FAB, *m*-nitrobenzyl alcohol): *m/z* calcd for $C_{36}H_{34}O_8$ 594.2254, found 594.2260.

(*M*,*M*)-(−)-[5]HELOL Analogue, 2. A solution of KOH (82 g, 1.45 mol) in degassed absolute ethanol (300 mL) was slowly added to a solution, cooled to 0 °C, of (*M*)-(−)-**9** (8.9 g, 0.015 mol) dissolved in THF (100 mL). After it was stirred at 0 °C for 2 h, acetic acid (115 mL, degassed by boiling under argon) was slowly added while the temperature was maintained at 0 °C, and the mixture was stirred for 20 min more, then poured into H_2O (1 L) and crushed ice (500 mL). Extraction (CH_2Cl_2, 600 mL), washing (ice water, 3 × 1 L), drying (Na_2SO_4), and concentration gave a yellow-brown solid, which was dissolved in CH_2Cl_2 (80 mL) and cooled to 0 °C. Ag_2O (5.3 g, 22.5 mmol) and Et_3N (1.3 mL) were added, whereupon the color immediately changed from brown to deep blue-green. After being stirred at 0 °C for 2 h, the mixture was filtered through Celite (which was then washed with CH_2Cl_2) and concentrated, giving a blue-green solid. This was mixed at 0 °C with zinc dust (24.6 g, 0.376 mol), acetone (100 mL), and acetic acid (4.3 mL), and the resulting mixture was stirred at 0 °C for 2 h. After it had been filtered through Celite (which was then washed with CH_2Cl_2 until the yellow material ceased to elute), washed with an equal volume of water (3×), dried ($MgSO_4$), and filtered, most of the solvent was evaporated and pentane (ca. 40 mL) was quickly added to precipitate the product, a light yellow solid. The yield over the three steps was 5.4 g (88%). ^{1}H NMR (CD_3CN, 400 MHz): δ 8.06−7.92 (m, 5H), 7.28 (s, 1H), 7.21−6.85 (br, 1H), 6.68 (s, 1H), 5.14 (s, 1H), 3.80 (s, 6H), 3.77 (s, 3H), 3.62 (s, 3H) ppm. ^{13}C NMR (CD_3CN, 100 MHz): δ 154.2, 145.4, 143.4, 129.0, 127.8, 127.1, 127.0, 126.6, 126.5, 125.4, 122.4, 121.4, 120.8, 118.3, 110.5, 61.9, 61.8, 57.2, 56.7 ppm. IR (KBr): 3523, 3401, 2996, 2935, 2836, 1612, 1517, 1459, 1398, 1345, 1287, 1261, 1242, 1215, 1165, 1119, 1108, 1081, 1005, 967, 843, 829 cm^{-1}. Mp: >60 °C (decomp). $[\alpha]_D$ −1924° (*c* 0.0026, CH_2Cl_2). HRMS (FAB, *m*-nitrobenzyl alcohol): *m/z* calcd for $C_{52}H_{42}O_{10}$ 826.2778, found 826.2803.

(*P*,*P*)-(+)-**2** (1.07 g, an 86% yield) was prepared by the same procedure starting from (*P*)-**9** (1.8 g, 0.003 mmol). Its ^{1}H, ^{13}C NMR spectra are identical to those of (*M*,*M*)-(−)-**2**. $[\alpha]_D$ +1936° (*c* 0.0026, CH_2Cl_2).

Analyses of Enantiomer Compositions. The following procedure is illustrative. A stock solution was prepared by adding CH_2Cl_2 to (*M*,*M*)-(−)-**2** (1.2 g, 1.4 mmol) and Et_3N (1.34 mL, 9.64 mmol) to bring the volume to 12 mL. A 200 μL aliquot of the solution, which contains (*M*,*M*)-(−)-**2** (20 mg, 0.024 mmol) and Et_3N (22 μL, 0.161 mmol), was added to an argon-filled 5 mL vial containing a catalytic amount of DMAP and a stirring bar. A solution of PCl_3 (200 μL of a 0.107 M solution in CH_2Cl_2, 0.021 mmol) was added, and the mixture was stirred at 25 °C for 15 min. The sample to be analyzed (0.029 mmol) was added, and the mixture was stirred for 2 h. An argon gas stream was used to evaporate the solvent, and the residue was quickly dissolved in a deuterated solvent (500 μL), pipetted into an NMR tube containing a capillary tube filled with 85 wt % H_3PO_4, and analyzed by proton-decoupled ^{31}P NMR spectroscopy (at 161.6 MHz). If the peaks were not sufficiently resolved, the solvent was evaporated with the aid of an argon gas stream, a new solvent was added, and the analysis was repeated. The spectra are assembled in the Supporting Information.

When the analysis was carried out with (*S*)-(−)-phenylethylamine (>99.0% ee) and the solvent was CD_3CN, (*M*,*M*)-(−)-**2** showed a single resonance at 151.09 ppm. When carried out with (*R*)-(+)-phenylethylamine (>99.0% ee), again a single resonance was observed, but at 150.86 ppm. With racemic phenylethylamine, both resonances were seen, and their intensities were equal (the measured ratio was 0.998). With a mixture of the two enantiomers [enriched in the (*R*)-enantiomer], prepared so as to have an ee of 50.1 ± 0.1%, again both resonances were recorded, and their intensities were 1.000 (151.09 peak):3.008 (150.86 peak), implying that the ee is 50.1 ± 0.8%. These results imply the ee in (*M*,*M*)-(−)-**2** to be >98%. The same procedure applied to (*P*,*P*)-(+)-**2** showed the ee of the major enantiomer to be >98%.

The materials analyzed were either commercially available (**10a**−**g**, **11a,b**, **11h**−**s**, **12a,b**, and **12g,h**) or synthesized (**11c**−**g** and **12c**−**f**) by procedures described previously.[1] The ^{31}P NMR chemical shifts (ppm) of the diastereomers formed by reaction with one of the chlorophosphites of **2** were as follows: **10a**, 151.09, 150.86 (CD_3CN); **10b**, 140.74, 139.58 ($CDCl_3$); 139.96, 138.22 (CD_3CN); **10c**, 132.90, 131.07 ($CDCl_3$); 132.42, 132.11 (CD_3CN); **10d**, 133.27, 132.69 ($CDCl_3$); 131.46, 131.05 (CD_3CN); **10e**, 142.94, 141.57 ($CDCl_3$); **10f**, 151.72, 150.49 ($CDCl_3$); **10g**, 144.87, 143.49 (CD_3CN); **11a**, 132.16, 131.15 (CD_3CN); **11b**, 129.90, 128.70 ($CDCl_3$); **11c**, 128.46, 128.27 ($CDCl_3$); **11d**, 129.22, 129.14 ($CDCl_3$); **11e**, 129.09, 128.73 ($CDCl_3$); 135.45, 134.88 (CD_3CN); **11f**, 128.66, 128.61 ($CDCl_3$); 135.01, 134.81 (CD_3CN); **11g**, 135.25, 135.10 (CD_3CN); **11h**, 129.04, 128.98 ($CDCl_3$); 133.70, 133.51 (CD_3CN); **11i**, 143.53, 140.92 ($CDCl_3$); **11j**, 142.02, 140.74 ($CDCl_3$); **11k**, 120.87, 120.51 ($CDCl_3$); 124.72, 124.51 (CD_3CN); **11l**, 128.79, 128.64 ($CDCl_3$); **11m**, 143.10, 142.42 ($CDCl_3$); **11n**, 138.77, 136.95 ($CDCl_3$); **11o**, 137.58, 137.24 ($CDCl_3$); **11p**, 135.16, 134.02 ($CDCl_3$); **11q**, 129.61, 129.65 ($CDCl_3$); 135.08, 133.25 (CD_3CN); **11r**, 150.44, 150.37, 149.30, 148.87 ($CDCl_3$); 149.60, 149.17, 147.56, 147.34 (CD_3CN); **11s**, 136.89, 135.88 (CD_3CN); **12a**, 139.33, 139.30 ($CDCl_3$); 136.58, 135.19 (CD_3CN); **12b**, −1.93, −2.71 ($CDCl_3$); **12c**, 136.81, 136.42 ($CDCl_3$); 135.21, 135.17 (CD_3CN); **12d**, 137.42, 136.97, −1.29, −1.33 ($CDCl_3$); 135.84, 135.46, −6.24, −6.30 (CD_3CN); **12f**, 136.63, 136.57 ($CDCl_3$); 135.35, 135.28 (CD_3CN); **12g**, 137.74, 137.45, −1.57, −1.87 ($CDCl_3$); **12h**, −1.81, −1.86 ($CDCl_3$).

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Supporting Information Available: ^{1}H, ^{13}C NMR, and IR spectra of **2**, **7**−**9**, and ^{31}P NMR spectra used to analyze the enantiomeric compositions of **10**−**12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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