all heavy atoms of both molecules were visible in the E map. Despite this promising result, attempts at solution were made in space groups $A2/m$ and Am but without success. The structure was refined by standard method using the program of XRAY72[17] (isotropic followed by anisotropic refinement of heavy atoms, finding H atoms in a difference map and finally refinement of all atoms with isotropic H thermal parameters). It proved necessary to carry out the refinement by alternately holding the parameters of one molecule constant and refining those of the other. The origin specification involves all the y parameters of one molecule and estimated standard deviations are given for all parameters. With 3228 observations (2273 with $I > \sigma(I)$) and a maximum $(\sin\theta)/\lambda$ of 0.6240 Å^{-1}, the final conventional R factor was 4.0%. The final atomic parameters and molecular dimensions are available as supplemental data, and the observed and calculated structure factors are available from J.V.S.

X-ray Crystallographic Data of Compound 4: $C_{15}H_{22}O_5$, mol wt = 282.34, $F(000)$ = 304, monoclinic $P2_1$, a = 5.465 (1), b = 13.752 (3), c = 9.831 (2) Å, and β = 101.71 (2). The unit cell volume is 723.4 (2) Å^3, Z = 2, and the calculated density is ρ_{calcd} = 1.296 mg mm^{-3}. A clear 0.21 mm × 0.07 mm × 0.08 mm crystal was used for data collection. The data were collected on a Nicolet R3m automated diffractometer with an incident-beam monochromator, λ = 1.54178 Å (Cu Kα), at T = 295 K. Lattice parameters were determined from 25 centered reflections between $16 \leq 2\theta \leq 55°$. The data collection range was $-6 \leq h \leq 3$, $0 \leq k \leq 15$, and $-10 \leq l \leq 10$ with $(\sin\theta)/\lambda_{max}$ = 0.56 Å^{-1}. Three standards were monitored every 60 reflections and exhibited a random variation of 3.4% over the data collection. A total of 1802 reflections were measured in the $\theta/2\theta$ mode with a scan width of 2.4°; scan rate was a function of count rate (4°/min minimum, 30°/min maximum). There were 1126 unique reflections, R_{int} = 0.038 from merging equivalent reflections, 966 observed with $F_o > 3\sigma(F_o)$. Lorentz and polarization corrections were applied, but no absorption correction was made; μ = 0.76 mm^{-1}.

The structure was solved by direct methods[18] with use of partial structure recycling.[19] The least-squares refinement program used the program SHELXTL.[20] In the block-cascade least squares the function minimized was $\sum w(|F_o| - |F_c|)^2$ where $w = 1/\sigma^2(|F_o| + g(F_o^2))$. The term $g(F_o^2)$ is included to account for random instrumental error (in the work g is estimated to be 0.0004). There were 194 parameters refined, including the atom coordinates and the anisotropic temperature factors for all non-H atoms. The y coordinate of O(1) was fixed to define the origin. Hydrogen atoms were fixed at ideal locations, and their isotropic temperature factors were fixed at 1.2 times the equivalent isotropic thermal parameters of the atom to which they were bonded. The coordinates and isotropic thermal parameter for H(16) were refined. The final residuals were R = 0.065 and R_w = 0.067 with an error in an observation of unit weight of S = 1.77 Å. Refinement of the other enantiomer gave residuals of R = 0.066 and R_w = 0.069 and S = 1.83, but the diffraction data were not accurate enough to determine the absolute configuration. The largest shift to error in the final cycle was 0.24, and the final difference Fourier excursions were −0.32 and 0.27 e Å^{-3}. Atomic scattering factors are from ref 21.

Supplementary Material Available: Tables of dimensions and coordinates for compounds **3** and **4** and ^{1}H and ^{13}C NMR spectra of compounds **2**, **3**, and **4** (32 pages). Ordering information is given on any current masthead page.

(16) Gilmore, C. J. "MITHRIL, A Computer Program for the Automatic Solution of Crystal Structures from X-Ray Data", University of Glasgow Glasgow, 1983.
(17) Stewart, J. M.; Kruger, G. J.; Ammon, H. L.; Dickinson, C.; Hall, S. R. X-Ray System-version of June 1972, Technical Report TR-192, University of Maryland.
(18) Karle, J.; Karle, I. L. *Acta Cryst.* **1966**, *21*, 849.
(19) Karle, J. *Acta Cryst.* **1968**, *B24*, 182.
(20) Sheldrick, G. M.; "SHELXTL 1980, Minicomputer Programs for Structure Determination", University of Gottingen: Federal Republic of Germany.
(21) "International Tables for X-Ray Crystallography"; Kynoch Press: Birmingham, England, 1975; Vol. IV.

The Design of Resolving Agents. Chiral Cyclic Phosphoric Acids

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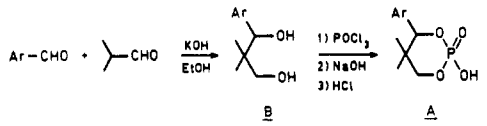
A systematic investigation has been started with the twofold purpose of synthesizing efficient resolving agents and of gaining an insight into the factors that contribute to successful resolutions. We report on the synthesis, resolution, and application of a number of chiral cyclic phosphoric acids. Among these acids, 4-(2-chlorophenyl)-5,5-dimethyl-2-hydroxy-1,3,2-dioxaphosphorinane 2-oxide (**7A**) is an efficient resolving agent, being useful for the resolution of amines and amino acids. Acid chloride **20** is a useful reagent for the determination of the ee of chiral amines. The absolute configuration of (−)-**7A** was determined through an X-ray structure determination of its salt with (−)-(*p*-hydroxyphenyl)glycine.

The rising demand for optically pure compounds has focused increasing attention on asymmetric synthesis. In spite of the successes achieved in this field, the classical resolution—through formation and separation of diastereoisomeric salts—remains the mainstay for the production of pure enantiomers, especially for their production on a multigram scale. To meet the demand for optically pure compounds the availability of a large and diverse group of resolving agents is necessary. Although in principle nature provides us with a virtually unlimited variety of resolving agents, the actual number of useful and readily available agents is barely a dozen.[1] The last decades have therefore seen the birth of synthetic resolving agents (where both enantiomers are usually available), which may give successful resolutions where natural resolving agents fail.[1] However, most of these synthetic resolving agents are semisynthetic (i.e. derived from natural, optically pure materials), and to our knowledge no systematic research toward the development of new resolving agents from *achiral* starting materials has been performed. In this paper we present the first results of our search for new

(1) Jacques, J.; Collet, A.; Wilen, S. H. "Enantiomers, Racemates, and Resolutions"; Wiley-Interscience: New York, 1981.

0022-3263/85/1950-4508$01.50/0

Scheme I



synthetic resolving agents. In addition to enlarging the number of available resolving agents, we were especially interested in the direct resolution of amino acids, i.e., through diastereoisomeric salt formation and separation, and in gaining an insight into the factors that govern resolutions.

On designing synthetic resolving agents, the following criteria have to be considered: (i) Strongly acidic and basic resolving agents are to be preferred over weakly acidic and basic agents (e.g., phosphoric and sulfonic acids are to be preferred over carboxylic acids) in order to increase the possibility of salt formation.[2] (ii) The stereocenter in the resolving agent should be close to the center of salt formation (proximity rule).[2] (iii) Rigidity is to be preferred over flexibility. A rigid resolving agent is preferred over a flexible agent, and in addition a resolving agent with several functionalities—which enhance rigidity and selectivity of the diastereoisomeric complex—is preferred over an agent lacking such functionalities. An example of this is the efficient resolution of biotin with arginine;[3] although the stereocenters of biotin and arginine seem to be far away from each other at first sight, secondary complexation will result in a rigid complex wherein the stereocenters are close to one another. (iv) Both enantiomers of the resolving agent should be readily available. (v) The resolving agent should be chemically and optically stable (under the conditions used for the formation, separation, and dissociation of diastereoisomeric salts and for recovery of the resolving agent).

None of these criteria is an absolute necessity, and therefore these criteria serve mainly as a guide in designing new resolving agents. In this paper we describe a series of chiral cyclic phosphoric acids of the general type **A**, which meet many of the criteria stated above. Since cyclic phosphoric acids are fairly strong acids (pK_A 2–3),[4] they might be expected to form salts with amines and amino acids. Indeed, several of these acids appear to be excellent resolving agents for amines and amino acids through diastereoisomeric salt formation.

Synthesis of Phosphoric Acids. The known aldol–Cannizzaro reaction between 2 equiv of isobutyraldehyde, 1 equiv of aromatic aldehyde, and 1 equiv of KOH in ethanol readily gives the 1-aryl-2,2-dimethyl-1,3-propanediols (**B**) (Scheme I) in good yields. Treatment of the diols with 1 equiv of $POCl_3$ in CH_2Cl_2 gives the cyclic phosphoric acid chlorides, which are hydrolyzed with NaOH in H_2O to give, after acidification, the desired cyclic phosphoric acids **A**. Table I shows the diols **B** and phosphoric acids **A** prepared in this manner (yields are nonoptimized). In the case of activated aromatic aldehydes the reaction with $POCl_3$ had to be performed in the presence of 2 equiv of Et_3N (for the diols **2B–5B**), whereas from the heteroaromatic diols **13B** and **14B** the phosphoric acids could not be obtained. None of the phosphoric acids **A** has been described in the literature. They are all solids (melting somewhere around 200 °C, usually with decomposition) and virtually insoluble in water and most organic solvents but quite soluble in polar solvents such as methanol and Me_2SO. The hydrolytic stability of the phosphoric acids was very good at room temperature (no apparent hydrolysis after stirring **7A** for 10 days with an excess of 1 N HCl or 1 N NaOH), but hydrolysis did occur at reflux temperatures (with a large excess of 2.5 N NaOH 60% of **1A** was recovered after 8 h, and similarly, 20% of **1A** was recovered after 6 h with 3 N HCl).

Table I

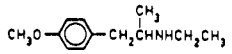
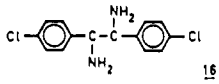
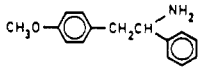
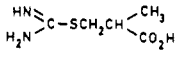
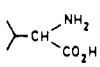
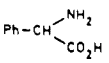
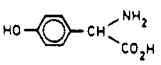
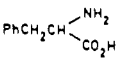
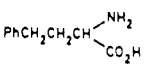
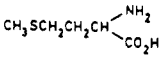
compd	substituent in ArCHO	yield of B[a]	yield of A	absolute $[\alpha]_{578}$
1	H	76[5]	100	60.2
2	2-OCH_3	oil[6]	74	63.8
3	4-OCH_3	49[7]	44	
4	3,4-OCH_2O	55[8]	67	
5	2-OEt	oil[6]	31[b]	60.9
6	4-CH_3	62[7]	66	
7	2-Cl	oil[8]	67	48.8
8	4-Cl	77[8]	86	59.5
9	2,4-Cl_2	oil[8]	61	49.2
10	2,6-Cl_2	oil	56	36.8
11	2-NO_2	42[6]	86	489[c]
12	3-NO_2	54	59	
13	Ar = 2-thienyl	78		
14	Ar = 2-furyl	72[9]		

[a] In cases where the diol was obtained as an oil, the crude diol was used for the synthesis of the phosphoric acids. In those cases the yield is based on the aromatic aldehyde. [b] Low yield is caused by loss of product in the exothermal hydrolysis step of the acid chloride. [c] The enantiomeric excess of this acid was not determined.

Resolution of Phosphoric Acids and Enantiomeric Excess Determination. Small-scale resolutions (1–2-mmol scale) were attempted with most of the cyclic phosphoric acids using (–)-ephedrine and (+)-2-amino-1-phenyl-1,3-propanediol as optically active bases (in the case of **5A**, **7A**, and **11A** (–)-(*p*-hydroxyphenyl)glycine was also used) and water/ethanol, methanol, ethanol, and ethyl acetate/ethanol as solvents. These test-tube solutions were then allowed to stand in the open air until crystals of the salt appeared (some water was usually added to the methanol and ethanol solutions when no crystals had appeared after most of the solvent had evaporated). In most cases crystals of the salt were obtained, and their rotation was measured. From the specific rotation of the salt it was estimated whether the small-scale resolutions had been successful, by using the not necessarily accurate additivity principle (specific rotation of the salt is the sum of the specific rotations of the components).[1] It was concluded from these experiments that most phosphoric acids could be resolved with either (–)-ephedrine or (+)-2-amino-1-phenyl-1,3-propanediol or with both (and with (–)-(*p*-hydroxyphenyl)glycine in the case of **5A**, **7A**, and **11A**). Larger scale, nonoptimized resolutions (0.2–1 mol) were then performed on the acids **2A**, **7A**, **9A**, **10A** (with (–)-ephedrine), **1A**, **8A** (with (+)-2-amino-1-phenyl-1,3-propanediol), **5A**, **7A**, and **11A** (with (–)-(*p*-hydroxyphenyl)glycine). In the case of **1A**, **5A**, **7A** (when the latter was resolved with (–)-(*p*-hydroxyphenyl)glycine), and probably **11A**, one crystallization was sufficient to obtain the optically pure diastereoisomeric salt, which after dissociation of the salt with hydrochloric acid directly gave

(2) Woodward, R. B.; Cava, M. P.; Ollis, W. D.; Hunger, A.; Daeniker, H. U.; Schenker, K. *Tetrahedron* **1963**, *19*, 247.
(3) Wolf, D. E.; Mozingo, R.; Harris, S. A.; Anderson, R. C.; Folkers, K. *J. Am. Chem. Soc.* **1945**, *67*, 2100.
(4) Kryuchkov, A. A.; Kozachenko, A. G.; Matrosov, E. I.; Kabachnik, M. I. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1978**, 1985. Cherkasov, R. A.; Ovchinnikov, V. V.; Pudovik, M. A.; Pudovik, A. N. *Usp. Khim.* **1982**, *51*, 1305.
(5) Reik, R. *Monatsh. Chem.* **1897**, *18*, 598.
(6) Herzog, O.; Kruh, O. *Monatsh. Chem.* **1900**, *21*, 1095.
(7) Kulka, K. South African Patent 6704670, 1969; *Chem. Abstr.* **1970**, *72*, P21476*m*.
(8) Kulka, K. U.S. Patent 3092639, 1963; *Chem. Abstr.* **1963**, *59*, P11336*d*.
(9) Lindauer, G. *Monatsh. Chem.* **1900**, *21*, 72.

Table II. Resolution of Amines and Amino Acids with Cyclic Phosphoric Acids

amine/amino acid	phosphoric acid	result[a] (small-scale)
 15	H, 4-Cl, 2-OEt, 2,4-Cl_2	–
	2-OCH_3	+
	2-Cl	++
 16	2-OCH_3	–
	2-Cl	+
	H, 2,4-Cl_2	++
 17	4-Cl	–
	H, 2-Cl	+
	2-OCH_3, 2-OEt, 2,4-Cl_2	++
 18	H, 4-Cl, 2-OEt	–
	2-OCH_3, 2-Cl, 2,4-Cl_2	+
	H, 4-Cl, 2-OCH_3, 2-OEt	–
	2-Cl	+
	H, 4-Cl, 2-Cl, 2-OCH_3	–
	H, 4-Cl	–
	2-OCH_3, 2-Cl, 2,4-Cl_2	++
	H, 4-Cl, 2-OEt, 2,4-Cl_2	–
	2-OCH_3	+
	2-Cl	++
 19	H, 2-OCH_3, 2-OEt, 2-Cl	–
	2,4-Cl_2	+
	2-OCH_3	–
	2-Cl	++

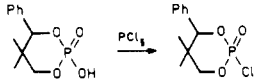
[a] No resolution, –; some resolution, +; excellent resolution, ++.

the optically pure phosphoric acid. From the filtrate of the crystallizations the optically impure phosphoric acids could be obtained. In most cases one recrystallization was sufficient to obtain the optically pure phosphoric acids. The acids **2A** and **8A–10A** were also obtained in an optically pure form; however, the resolution of these acids did not proceed as efficiently as those of the acids **1A**, **5A**, **7A**, and **11A** (cf. Experimental Section). Yet, future resolutions of **2A** and **9A** with (–)-(*p*-hydroxyphenyl)-glycine are expected to proceed very easily (on the basis of the similar resolutions of **5A**, **7A**, and **11A** and of the resolution of (±)-(*p*-hydroxyphenyl)glycine with **2A** and **9A**, cf. below). The absolute rotations of the phosphoric acids are given in Table I and obviously refer to optically pure compounds.

The enantiomeric excesses of the resolved phosphoric acids could be determined by reduction of the phosphoric acids to the parent diols with lithium aluminum hydride and subsequent ^{1}H NMR investigation of these diols in the presence of the chiral shift reagent Eu(hfc)$_3$. This readily established the enantiomeric excess of the diols (and, hence, of the phosphoric acids), because several signals of the diols were very well resolved with Eu(hfc)$_3$. Of course, the simplicity of the ^{1}H NMR spectra of the diols makes these diols very suitable for shift reagent studies. In addition, the absolute configuration of the (–)-diol **1B** is known to be *R*;[10] therefore the absolute configuration of the corresponding (–)-phosphoric acid **1A** is also *R*.

(10) Guetté, M.; Capillon, J.; Guetté, J.-P. *Tetrahedron* **1973**, *29*, 3659.

Application of the Phosphoric Acids as Resolving Agents. Resolution attempts on a 1–2-mmol scale indicated that the cyclic phosphoric acids were efficient resolving agents (Table II). Several successful 1–2-mmol resolutions (again, based on the additivity principle) were then scaled up to 0.01–0.1 mol (cf. Experimental Section). In almost all larger scale resolutions one crystallization furnished optically pure salts, thus establishing these phosphoric acids as excellent resolving agents. Only in the case of phenylglycine did resolution fail. Valine, the isothiouronium salt **18**,[11] and homophenylalanine **19**[12] were not completely resolved. Valine could be resolved to an enantiomeric excess of ≥40% (several experiments indicated that the optimum conditions for this resolution had not yet been found), the internal salt **18** was resolved to an enantiomeric excess of 50% (no change in rotation of the salt after recrystallization), and homophenylalanine **19** was resolved to an enantiomeric excess of 25%. The resolution of amino acids was hampered occasionally by solubility problems, because the phosphoric acids are soluble in (m)ethanol and almost insoluble in water, the reverse generally being true for amino acids; this necessitates the use of a solvent mixture for these resolutions, and in those cases where no efficient salt formation occurs (phenylgycine, and to a lesser extent valine and homophenylalanine **19**) it is either the amino acid or the phosphoric acid which precipitates (depending on the composition of the solvent). For example, although the salt from D-(–)-phenylglycine and (–)-**7A** could be prepared from the two components, we were unable to effect selective crystallization of this salt from an equimolar mixture of (±)-phenylglycine and (–)-**7A** in water/ethanol. Dissociation of the diastereoisomeric salts with either acid (amino acids, some amines) or base (amines) allows an easy separation between the amino acid or amine and the phosphoric acid, the phosphoric acid being almost insoluble in aqueous acid and reasonably soluble in aqueous base. Resolved amines and amino acids were ≥95% enantiomerically pure (amine **15** was ≥85% enantiomerically pure), as deduced from the specific rotations of the amino acids, from the indirect DSC method applied to the stilbenediamine **16**[1,13,14] or from the NMR spectra of the diastereoisomeric amides derived from the enantiomerically pure phosphoric acid chloride **20** and the amines **15** and **17**. Acid chloride **20** was readily prepared from the corresponding phosphoric acid **1A** by reaction with phosphorus pentachloride; this acid chloride then reacts with primary



1A **20**

amines (THF, Et_3N, reflux, 16 h), secondary amines (*n*-BuLi/THF, room temperature, 16 h), and alcohols (*n*-BuLi/THF, room temperature, 16 h) to give the corresponding amides or esters. With (±)-**15** and (±)-**17**, two diastereoisomeric amides were obtained. In the case of (±)-**17** the decoupled ^{31}P NMR spectrum showed a 0.54 ppm difference between the amides, and in the case of (±)-**15** in the ^{31}P NMR spectrum no difference was observed; however, the ^{1}H NMR spectrum showed a 0.30 ppm difference (benzylic proton).[15] Hence, at least in the

(11) Kataev, E. G.; Barinova, L. K. *Dokl. Akad. Nauk SSSR* **1961**, *141*, 1373; *Chem. Abstr.* **1962**, *56*, 12727*i*.
(12) Weller, H. N.; Gordon, E. M. *J. Org. Chem.* **1982**, *47*, 4160.
(13) Bosgraaf, A.; Wynberg, H., unpublished results.
(14) Fouquey, C.; Jacques, J. *Tetrahedron* **1967**, *23*, 4009. Fouquey, C.; Leclercq, M. *Tetrahedron* **1970**, *26*, 5637.

cases we have studied, phosphoric acid chloride **20** appears to be a useful, air-stable reagent for the ee determination of amines and possibly alcohols.[16]

Discussion

From the resolutions performed with the phosphoric acids the following trends were observed:

(i) The presence of an ortho substituent in the aromatic ring is beneficial for most resolutions (although for some amines the unsubstituted phosphoric acid **1A** works as well). In addition to the inherent rigidity of these acids provided by the vicinal phenyl and geminal methyl groups in a six-membered ring (NMR data show that only one isomer is present, with the phenyl group in an equatorial position[17]), the presence of an ortho substituent inhibits the rotational freedom of the phenyl ring (according to space-filling models), thereby creating even greater rigidity and thus restricting the number of possible conformations for the acid and for the salts derived from it, enhancing the difference between the two diastereoisomeric salts. In addition, the presence of an ortho substituent may allow for additional complexation between phosphoric acid and amine or amino acid upon salt formation.

(ii) Valine excepted, the combination of L-amino acids and the (+)-2-chloro compound yields the less soluble salt (also L-homophenylalanine **19** combined with the (+)-2,4-dichloro compound gives the less soluble salt). It seems therefore that the resolution of amino acids by the (+)-2-chloro compound (or the (+)-2,4-dichloro compound) is fairly independent of the nature of the side chain in the amino acid.

(iii) (*p*-Hydroxyphenyl)glycine is resolved by all ortho-substituted phosphoric acids—assuming that reciprocal resolution will take place—irrespective of the nature of the ortho substituent (whether this substituent is 2-chloro, 2-methoxy, 2,4-dichloro, 2-nitro, or 2-ethoxy). It appears therefore that the resolution of (*p*-hydroxyphenyl)glycine is independent of the nature of the ortho substituent in the phosphoric acid (hydrogen excepted).

Combining ii and iii leads us to the conclusion that there is no interaction between the side chain of the amino acid and the aromatic ring of the phosphoric acid. Hence, electronic effects play a minor role in these resolutions and the major role is claimed by the rigidity provided by the presence of a 2-substituted phenyl group (cf. i).

Further support for these conclusions comes from an X-ray structure determination of the P salt of the (−)-2-chloro compound and D-(−)-(*p*-hydroxyphenyl)glycine (Figure 1) . This structure determination confirms that the (−)-2-chloro compound has the *S* configuration (as was expected from the absolute configuration of **1A**) and that there is no interaction between the aromatic rings of the two components of this salt (as inferred from the distance between the aromatic groups). Some other features following from this X-ray structure are the presence of an axial P=O bond (whereas in most 2-oxo-1,3,2-dioxaphosphorinanes the P=O bond is in an equatorial position[17]) and the presence of hydrogen bonds between POH and NH_2 and between P=O and COH, respectively. Also evident from the X-ray parameters is the strong thermal vibration of the 2-chlorophenyl portion of the molecule.

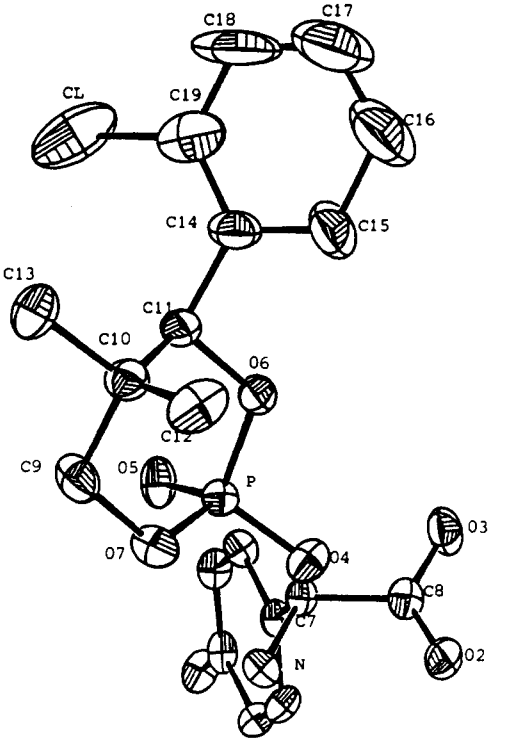


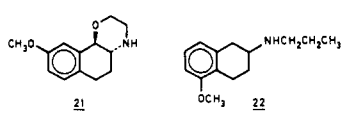
Figure 1. ORTEP drawing of the salt from (−)-(*p*-hydroxyphenyl)glycine and (−)-**7A**.

We have now established factors that play an important role in the resolutions performed with the phosphoric acids and the structure of one of the salts derived from the phosphoric acid (−)-**7A**. Further quantification of resolutions with the cyclic phosphoric acids is under investigation.[18,19] It appears to us not too farfetched to predict that further careful examination and systematic analysis of both NMR differences (for covalent diastereoisomers such as amides) and X-ray structure differences (for the corresponding diastereoisomeric salts) will show a trend pointing to a "more compact", "best-fit" diastereoisomeric salt and a "looser" diastereoisomeric salt.[20]

Experimental Section

General Remarks. Solvents and reagents were reagent grade and were used without further purification. In most resolutions, seed crystals were added from time to time to the stirred solution of the components until crystallization started. Optical rotations were measured at room temperature (20 °C) on a Perkin-Elmer 241 polarimeter; unless stated otherwise, methanol was used as the solvent with $c = 0.5$. Melting points were determined on a Mettler FP-2 melting point apparatus. ^1H NMR spectra were recorded on a Perkin-Elmer R-24B spectrophotometer with $CDCl_3$ as solvent (60 MHz). ^1H chemical shifts are reported in δ units

(15) ^{31}P chemical shift differences for some other compounds were: α-methylbenzylamine, 0.70 ppm; menthol, 0.05 ppm; 2-butanol, 0.00 ppm. After submission of this manuscript the amines **21** and **22** have been



21 22

resolved with **7A** (again, one crystallization furnished optically pure products; in the case of **21** resolution with **1A** was more convenient). The enantiomeric excess of the amines could be determined through ^{31}P NMR spectroscopy using the adduct with **20**, $\Delta\delta$ being 0.18 and 0.09 ppm, respectively.

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(ppm) relative to internal Me_4Si (δ 0). ^{31}P NMR spectra were recorded on a Nicolet NT-200 spectrometer. IR spectra were recorded on a Unicam SP-200 infrared spectrophotometer. Elemental analyses were performed in the microanalytical section of this department. Crystallographic studies were performed by F. van Bolhuis of the Department of Chemical Physics, University of Groningen. His contribution is gratefully acknowledged.

General Procedure for the Preparation of 1-(Hetero)-aryl-2,2-dimethyl-1,3-propanediols. To a mixture of the (hetero)aromatic aldehyde (1 mol) and isobutyraldehyde (2 mol) is added slowly a solution of 85% KOH (1 mol) in absolute ethanol (900 mL). An exothermic reaction starts; when the temperature of the mixture has reached 50 °C, the flask is cooled by a water bath. Usually the temperature rises to ca. 70 °C and then drops again. When the temperature has fallen to ca. 55 °C, the remainder of the KOH solution is added rapidly (ca. 10 min). The reaction mixture is heated at 50–60 °C for 5 h and then evaporated at aspirator vacuum. Water (1 L) is added to the remaining residue, and this mixture is extracted with 3 × 300 mL of chloroform. After washing with 0.5 L of water, drying over Na_2SO_4, and evaporation, the crude product is obtained, which can be purified by crystallization from toluene/hexane (solid diols) or distilled at 0.1 mmHg (liquid diols). In the case of liquid diols the crude, nonpurified product was used as such for the next step.

Yields of the diols are shown in Table I.

2,2-Dimethyl-1-(2-thienyl)-1,3-propanediol (**13B**): mp 62–63 °C. Anal. Calcd for $C_9H_{14}O_2S$: C, 58.03; H, 7.57; S, 17.22. Found: C, 57.98; H, 7.47; S, 17.21.

2,2-Dimethyl-1-(3-nitrophenyl)-1,3-propanediol (**12B**): mp 98.5–99.5 °C. Anal. Calcd for $C_{11}H_{15}NO_4$: C, 58.65; H, 6.71; N, 6.22. Found: C, 58.58; H, 6.68; N, 6.08.

Relevant ^1H NMR data for diols: **1B**, 0.85 (2 s, 6 H), 3.5 (s, 2 H), 4.6 (s, 1 H), 7.3 (s, 5 H); **2B**, 0.85 (2 s, 6 H), 3.35 (s, 2 H), 3.8 (s, 3 H), 5.05 (s, 1 H), 6.6–7.5 (m, 4 H); **3B**, 0.85 (s, 6 H), 3.45 (s, 2 H), 3.75 (s, 3 H), 4.5 (s, 1 H), 6.6–7.3 (m, 4 H); **4B**, 0.8 (s, 6 H), 3.4 (s, 2 H), 4.45 (s, 1 H), 5.85 (s, 2 H), 6.6 (s, 2 H), 6.7 (s, 1 H); **5B**, 0.85 (2 s, 6 H), 1.4 (t, J = 7 Hz, 3 H), 3.35 (s, 2 H), 3.9 (q, J = 7 Hz, 2 H), 5.0 (s, 1 H), 6.6–7.5 (m, 4 H); **6B**, 0.8 (2 s, 6 H), 2.3 (s, 3 H), 3.5 (s, 2 H), 4.5 (s, 1 H), 7.1 (s, 4 H); **7B**, 0.85 (2 s, 6 H), 3.45 (s, 2 H), 5.15 (s, 1 H), 7.0–7.6 (m, 4 H); **8B**, 0.8 (s, 6 H), 3.45 (s, 2 H), 4.5 (s, 1 H), 7.2 (s, 4 H); **9B**, 0.85 (2 s, 6 H), 3.45 (s, 2 H), 5.1 (s, 1 H), 7.0–7.5 (m, 3 H); **10B**, 1.0 (2 s, 6 H), 3.25–3.8 (AB, J = 11 Hz, 2 H), 5.5 (s, 1 H), 7.0–7.3 (m, 2 H); **11B**, 0.8 (s, 6 H), 3.5 (s, 2 H), 5.55 (s, 1 H), 7.2–7.9 (m, 4 H); **12B**, 0.85 (s, 6 H), 3.5 (s, 2 H), 4.7 (s, 1 H), 7.1–8.2 (m, 4 H); **13B**, 0.9 (2 s, 6 H), 3.25–3.65 (AB, J = 10 Hz, 2 H), 4.85 (s, 1 H), 6.8–7.3 (m, 3 H); **14B**, 0.85 (s, 6 H), 3.1–3.6 (AB, J = 11 Hz, 2 H), 4.45 (s, 1 H), 6.0–6.2 (m, 2 H), 7.1 (br s, 1 H).

General Procedures for the Preparation of Cyclic Phosphoric Acids. (a) To a warm solution of the diol (1 mol) in 400 mL of CH_2Cl_2 is added over 30–60 min a solution of phosphoryl chloride (1.1 mol) in 200 mL of CH_2Cl_2. The mixture is heated under reflux for 3 h and then evaporated. The residue (sometimes solidifying) is added in 15–30 min to a 95 °C solution of 120 g of NaOH in 1200 mL of water at such a rate that the strongly exothermic reaction is kept under control (at temperatures below 90 °C the reaction does not proceed due to the insolubility of the phosphoric acid chloride in water). In all cases, except for the 2,4-dichloro compound **9B**, a clear solution was obtained at the end of the addition. After being stirred for 15 min the solution was cooled to ca. 60 °C (often causing the precipitation of the sodium salt of the phosphoric acid) and then acidified with 250 mL of concentrated hydrochloric acid to precipitate the phosphoric acid. After the solution cools to room temperature, the product is sucked off, washed with water and ether, and dried at 80 °C. The product thus obtained is pure enough for further manipulations but can be recrystallized from ethanol or ethanol/water.

(b) To a solution of the diol (1 mol) and triethylamine (2.1 mol) in 500 mL of CH_2Cl_2 is added a solution of phosphoryl chloride (1.05 mol) in 250 mL of CH_2Cl_2 (with cooling, in 30–60 min). The mixture is heated under reflux for 3 h and then extracted with 2 × 250 mL of water. The water layers are extracted with 150 mL of CH_2Cl_2. The CH_2Cl_2 layers are dried and evaporated to give the phosphoric acid chloride, which is added to a hot NaOH solution as described above. The phosphoric acid is obtained after acidification, as described above.

Physcial data (^1H NMR spectra recorded with $CDCl_3$ and usually a small amount of Me_2SO as solvent) are as follows.

1A: mp 224–224.5 °C; ^1H NMR 0.8 (s, 3 H), 1.0 (s, 3 H), 3.4–4.4 (m, 2 H), 5.2 (br s, 1 H), 7.3 (s, 5 H). Anal. Calcd for $C_{11}H_{15}O_4P$: C, 54.55; H, 6.24; P, 12.79. Found: C, 54.42; H, 6.17; P, 12.72.

2A: mp 204–205 °C; ^1H NMR 0.7 (s, 3 H), 1.05 (s, 3 H), 3.5–4.5 (m), 3.8 (s, 5 H), 5.85 (br s, 1 H), 6.7–7.5 (m, 4 H). Anal. Calcd for $C_{12}H_{17}O_5P$: C, 52.94; H, 6.29; P, 11.38. Found: C, 52.83; H, 6.33; P, 11.19.

3A: mp 205–206 °C; ^1H NMR 0.75 (s, 3 H), 1.0 (s, 3 H), 3.4–4.4 (m), 3.75 (s, 5 H), 5.1 (br s, 1 H), 6.7–7.3 (m, 4 H). Anal. Calcd for $C_{12}H_{17}O_5P$: C, 52.94; H, 6.29; P, 11.38. Found: C, 52.96; H, 6.30; P, 11.49.

4A: mp 200–201.5 °C; ^1H NMR 0.75 (s, 3 H), 1.0 (s, 3 H), 3.4–4.4 (m, 2 H), 5.1 (br s, 1 H), 5.9 (s, 2 H), 6.75 (2 s, 3 H). Anal. Calcd for $C_{12}H_{15}O_6P$: C, 50.35; H, 5.28; P, 10.82. Found: C, 50.21; H, 5.28; P, 10.71.

5A: ^1H NMR 0.7 (s, 3 H), 1.05 (s, 3 H), 1.4 (t, J = 7 Hz, 3 H), 3.3–4.4 (m, 4 H), 5.7 (br s, 1 H), 6.7–7.5 (m, 4 H). Anal. Calcd for $C_{13}H_{19}O_5P$: C, 54.54; H, 6.69; P, 10.82. Found: C, 54.31; H, 6.73; P, 10.58.

6A: mp 219–221 °C; ^1H NMR 0.75 (s, 3 H), 1.0 (s, 3 H), 3.5–4.5 (m, 2 H), 5.15 (br s, 1 H), 7.1 (s, 4 H). Anal. Calcd for $C_{12}H_{17}O_4P$: C, 56.24; H, 6.67; P, 12.09. Found: C, 56.20; H, 6.71; P, 12.09.

7A: ^1H NMR 0.8 (s, 3 H), 1.1 (s, 3 H), 3.4–4.4 (m, 2 H), 5.4 (br s, 1 H), 7.1–7.6 (m, 4 H). Anal. Calcd for $C_{11}H_{14}ClO_4P$: C, 47.75; H, 5.10; Cl, 12.82; P, 11.20. Found: C, 47.65; H, 5.08; Cl, 13.09; P, 11.15.

8A: mp 222–223 °C; ^1H NMR 0.8 (s, 3 H), 1.0 (s, 3 H), 3.5–4.5 (m, 2 H), 5.2 (br s, 1 H), 7.25 (s, 4 H). Anal. Calcd for $C_{11}H_{14}ClO_4P{\cdot}H_2O$: C, 44.83; H, 5.47; Cl, 12.03; P, 10.51. Found: C, 44.75; H, 5.56; Cl, 11.91; P, 10.38.

9A: ^1H NMR 0.8 (s, 3 H), 1.05 (s, 3 H), 3.3–4.4 (m, 2 H), 5.65 (br s, 1 H), 7.1–7.4 (m, 3 H). Anal. Calcd for $C_{11}H_{13}Cl_2O_4P$: C, 42.47; H, 4.21; Cl, 22.79; P, 9.96. Found: C, 42.29; H, 4.25; Cl, 22.93; P, 9.91.

10A: ^1H NMR 0.9 (s, 3 H), 1.25 (s, 3 H), 3.3–4.4 (m, 2 H), 6.0 (br s, 1 H), 7.2–7.4 (m, 3 H). Anal. Calcd for $C_{11}H_{13}Cl_2O_4P$: C, 42.47; H, 4.21; Cl, 22.79; P, 9.96. Found: C, 42.34; H, 4.32; Cl, 22.90; P, 9.78.

11A: ^1H NMR 0.8 (s, 3 H), 1.0 (s, 3 H), 3.4–4.4 (m, 2 H), 6.15 (br s, 1 H), 7.3–7.9 (m, 4 H). Anal. Calcd for $C_{11}H_{14}NO_6P$: C, 46.00; H, 4.91; N, 4.88; P, 10.79. Found: C, 45.99; H, 4.94; N, 4.91; P, 11.01.

12A: mp 209–211 °C; ^1H NMR 0.8 (s, 3 H), 1.0 (s, 3 H), 3.5–4.5 (m, 2 H), 5.35 (br s, 1 H), 7.4–8.3 (m, 3 H). Anal. Calcd for $C_{11}H_{14}NO_6P$: C, 46.00; H, 4.91; N, 4.88; P, 10.79. Found: C, 45.72; H, 4.88; N, 4.87; P, 10.84.

Resolution of 5,5-Dimethyl-2-hydroxy-4-phenyl-1,3,2-dioxaphosphorinane 2-Oxide (1A). A mixture of 128.0 g of crude **1A** (0.529 mol), 90.0 g of (+)-2-amino-1-phenyl-1,3-propanediol (0.539 mol), and 330 mL of 96% ethanol is heated until solution took place. The heating mantle is removed, and the solution is allowed to cool to room temperature with stirring. After the mixture stirs for 5 h, the product is sucked off and washed with ether to give 86.1 g of the salt (0.211 mol, 40%) with $[\alpha]_{578}$ −15.1°. This salt is stirred for 3 h with 500 mL of water and 150 mL of concentrated hydrochloric acid, then filtered, washed with water, and dried to give 48.7 g of the acid **1A** (0.201 mol, 38%) with $[\alpha]_{578}$ −60.0°. The filtrate from the crystallization is stirred for 3 h with 150 mL of concentrated hydrochloric acid, then filtered, washed with water, and dried to give 64.9 g of **1A** (0.268 mol, 51%) with $[\alpha]_{578}$ +47.9°. From the filtrate another 6.7 g of **1A** (0.028 mol, 5%) with $[\alpha]_{578}$ −1.2° can be obtained. Recrystallization of 64.9 g of **1A** from ethanol gives 51.8 g of **1A** (0.214 mol, 40%) with $[\alpha]_{578}$ +62.5° (mp 230–231 °C). The filtrate, after almost complete evaporation and addition of water, gives 13.8 g of **1A** (0.057 mol, 11%) with $[\alpha]_{578}$ −12.1°. On the basis of the completely identical IR spectra of optically pure and racemic **1A**, as well as on the crystallization behavior of optically active **1A**, it was concluded that **1A** is a conglomerate.

Resolution of 5,5-Dimethyl-2-hydroxy-4-(2-methoxyphenyl)-1,3,2-dioxaphosphorinane 2-Oxide (2A). A mixture of 173.3 g of crude acid **2A** (0.637 mol), 102.3 g of (−)-ephedrine (0.619 mol), and 360 mL of 96% ethanol is heated to solution. The heating mantle is removed, and the solution is allowed to

cool to room temperature with stirring. After standing overnight, the salt, having $[\alpha]_{578}$ +6.7°, is sucked off, washed with ether, and then recrystallized from 360 mL of 96% ethanol to give 80.0 g of the salt (0.183 mol, 29%) with $[\alpha]_{578}$ +9.6°. Stirring with 40 mL of concentrated hydrochloric acid and 170 mL of water for 5 h, followed by filtration and washing with water, gives 48.8 g of **2A** (0.179 mol, 28%) with $[\alpha]_{578}$ +58.5°. The first filtrate, on evaporation and treatment with hydrochloric acid, gives 73.0 g of **2A** (0.268 mol, 42%) with $[\alpha]_{578}$ −38.2°. Recrystallization from ethanol gives 32.2 g of **2A** (0.118 mol, 19%) with $[\alpha]_{578}$ −63.8° (mp 195–197 °C). The second filtrate, on evaporation and treatment with hydrochloric acid gives 28.0 g of **2A** (0.103 mol, 16%) with $[\alpha]_{578}$ −11.5°.

Resolution of 5,5-Dimethyl-4-(2-ethoxyphenyl)-2-hydroxy-1,3,2-dioxaphosphorinane 2-Oxide (5A). A mixture of 115.4 g of crude acid **5A** (0.403 mol), 68.0 g of (−)-(*p*-hydroxyphenyl)glycine (0.407 mol), 700 mL of water, and 700 mL of absolute ethanol is heated to effect solution. The heating mantle is removed, and the solution is allowed to cool to room temperature with stirring. After 5 h the salt is sucked off, washed with water, and dried to give 66.8 g of **5A** (0.147 mol, 37%), $[\alpha]_{578}$ −98.5°. Hydrolysis with 30 mL of concentrated hydrochloric acid and 300 mL of water (5 h) gives 42.0 g of **5A** (0.147 mol, 37%) with $[\alpha]_{578}$ −60.9°. Treatment of the filtrate from the crystallization with hydrochloric acid gives 61.6 g of **5A** (0.215 mol, 53%) with $[\alpha]_{578}$ +37.0°. Optically pure **5A** has mp 215.5–216.5 °C.

Resolution of 4-(2-Chlorophenyl)-5,5-dimethyl-2-hydroxy-1,3,2-dioxaphosphorinane 2-Oxide (7A). A mixture of 169.9 g of crude acid **7A**, containing a small amount of optically impure (+)-acid (0.615 mol), 102.7 g of (−)-(*p*-hydroxyphenyl)-glycine (0.615 mol), 1030 mL of 96% ethanol, and 800 mL of water is heated to effect solution. The heating mantle is removed, and the solution is allowed to cool to room temperature with stirring. After the solution is stirred overnight, the salt is sucked off, washed with 300 mL of water, and dried to give 103.6 g of the salt (0.234 mol, 38%) with $[\alpha]_{578}$ −95.7°. This salt is stirred for 6 h with 105 mL of concentrated hydrochloric acid and 470 mL of water, then sucked off, washed with water, and dried to give 58.8 g of **7A** (0.213 mol, 35%) with $[\alpha]_{578}$ −49.3°. The filtrate from the crystallization (including the water used for washing) is stirred for 7 h with 150 mL of concentrated hydrochloric acid to give 74.3 g of **7A** (0.269 mol, 44%) with $[\alpha]_{578}$ +48.9°. From this filtrate another 21.0 g of **7A** (0.076 mol, 12%) with $[\alpha]_{578}$ +16.7° can be obtained after partial evaporation. Optically pure **7A** has mp 225.5–227 °C.

Resolution of 4-(4-Chlorophenyl)-5,5-dimethyl-2-hydroxy-1,3,2-dioxaphosphorinane 2-Oxide (8A). A mixture of 63.3 g of crude acid **8A** (0.229 mol), 40.0 g of (+)-2-amino-1-phenyl-1,3-propanediol (0.239 mol), 650 mL of water, and 110 mL of 96% ethanol is heated to solution and then allowed to cool to room temperature with stirring. After the solution stands overnight, there is obtained 29.3 g of the salt (0.066 mol, 29%) with $[\alpha]_{578}$ +35.0°. Treatment with hydrochloric acid gives 19.50 g of **8A** with $[\alpha]_{578}$ +30.9°, which on recrystallization from methanol/water gives 9.41 g of **8A** (0.034 mol, 15%) with $[\alpha]_{578}$ +59.5° (mp 217–218 °C). The filtrate and an equivalent amount of the (+)-amine are combined with the filtrate from the first crystallization, this mixture is evaporated, and the residue is recrystallized from a mixture of 200 mL of methanol and 250 mL of water to give after standing overnight 10.0 g of salt (0.022 mol, 10%) with $[\alpha]_{578}$ −20.5°. Treatment of this salt with hydrochloric acid gives 6.0 g of **8A** (0.022 mol, 9%) with $[\alpha]_{578}$ −58.1°. On the basis of the completely identical IR spectra of optically pure and racemic **8A**, as well as on the crystallization behavior of optically active **8A**, it was concluded that **8A** is a conglomerate.

Resolution of 4-(2,4-Dichlorophenyl)-5,5-dimethyl-2-hydroxy-1,3,2-dioxaphosphorinane 2-Oxide (9A). A mixture of 285.5 g of crude acid **9A** (0.918 mol), 155.0 g of (−)-ephedrine (0.939 mol), and 500 mL of 96% ethanol is heated to solution. The heating mantle is removed, and the solution is allowed to cool to room temperature with stirring. After the solution is stirred for 5 h and stands overnight, the salt is sucked off and washed with ether to give 204 g of the salt (0.429 mol, 47%) with $[\alpha]_{578}$ −5.2°. Recrystallization from 430 mL of 96% ethanol gives 118.5 g of salt (0.249 mol, 27%) with $[\alpha]_{578}$ +6.2°. Treatment with hydrochloric acid then gives 76.4 g of **9A** (0.246 mol, 27%) with $[\alpha]_{578}$ +46.6°; this on recrystallization from aqueous ethanol gives **9A** with $[\alpha]_{578}$ +49.2° (mp 238.5–240.5 °C). From the first filtrate there can be obtained 52.5 g of salt (0.110 mol, 12%) with $[\alpha]_{578}$ −44.0° after partial evaporation of this filtrate (ca. 250 mL of ethanol removed). Treatment of this salt with hydrochloric acid gives 33.7 g of **9A** (0.108 mol, 12%) with $[\alpha]_{578}$ −43.2°.

Resolution of 4-(2,6-Dichlorophenyl)-5,5-dimethyl-2-hydroxy-1,3,2-dioxaphosphorinane 2-Oxide (10A). A mixture of 168.1 g of crude acid **10A** (0.541 mol), 91.0 g of (−)-ephedrine (0.552 mol), and 350 mL of 96% ethanol is heated to solution. The heating mantle is removed, and the solution is allowed to cool to room temperature with stirring. After 7 h the salt is sucked off and washed with ether to give 70.5 g of the salt (0.148 mol, 27%) with $[\alpha]_{578}$ +1.8°. Treatment of this salt with 90 mL of concentrated hydrochloric acid and 400 mL of water gives the acid **10A** with $[\alpha]_{578}$ +30.3°. Recrystallization from aqueous ethanol gives 37.5 g of **10A** (0.121 mol, 22%) with $[\alpha]_{578}$ +36.8° (mp 256–258 °C). The first filtrate is evaporated, and the residue is recrystallized from a mixture of 250 mL of 96% ethanol and 150 mL of ether to give 29.6 g of the salt (0.062 mol, 11%) with $[\alpha]_{578}$ −12.8° (from this salt there is obtained 17.8 g of **10A** (0.057 mol, 11%) with $[\alpha]_{578}$ +9.7°). The filtrate after evaporation, treatment with hydrochloric acid, and recrystallization from aqueous ethanol gives 48.0 g of **10A** (0.154 mol, 29%) with $[\alpha]_{578}$ −36.1°.

Resolution of 5,5-Dimethyl-2-hydroxy-4-(2-nitrophenyl)-1,3,2-dioxaphosphorinane 2-Oxide (11A). A mixture of 58.6 g of crude acid **11A** (0.204 mol), 34.2 g of (−)-(*p*-hydroxyphenyl)glycine (0.205 mol), 300 mL of water, and 300 mL of 96% ethanol is heated to solution. The heating mantle is removed, and the solution is allowed to cool to room temperature with stirring. After stirring overnight, there is obtained 40.5 g of the salt (0.089 mol, 44%) with $[\alpha]_{578}$ −353°. Treatment with hydrochloric acid gives 23.9 g of acid **11A** (0.083 mol, 41%) with $[\alpha]_{578}$ −463°. The first filtrate is treated with hydrochloric acid to give 27.7 g of acid **11A** (0.097 mol, 47%) with $[\alpha]_{578}$ +409°, which after recrystallization from ethanol gives 17.8 g of **11A** (0.062 mol, 30%) with $[\alpha]_{578}$ +489° (mp 229.5–230.5 °C). Phosphoric acid **11A** is light-sensitive.

Resolution of *N*-Ethyl-4-methoxy-α-methylbenzeneethanamine (15). A mixture of 9.8 g of amine **15**[21] (50.8 mmol), 14.0 g of (−)-**7A** (50.6 mmol), 25 mL of water, and 10 mL of 96% ethanol is heated to give a solution. The solution is stirred for 6 h at room temperature and then allowed to stand overnight. There is obtained 4.75 g of the salt (10.1 mmol, 20%) with $[\alpha]_{578}$ −23.7°, which is stirred for 2 h with 4 g of sodium hydroxide in 100 mL of water. After chloroform extraction (2 × 75 mL), washing with water (100 mL), drying, evaporation, and Kugelrohr distillation [90 °C (0.1 mmHg)], there is obtained 1.89 g of **15** (9.8 mmol, 19%) with $[\alpha]_{578}$ +26.4°.

Resolution of 1,2-Bis(4-chlorophenyl)-1,2-ethanediamine (16). A mixture of 12.5 g (44.5 mmol) of racemic diamine **16**[13] and 12.5 g of (−)-**1A** (44.6 mmol) is dissolved in 75 mL of 96% ethanol. The solution is allowed to cool to room temperature with stirring. After 6 h the product is collected and washed with ether/ethanol and ether. The yield is 6.38 g (12.2 mmol, 27%) of the salt with $[\alpha]_{578}$ +63.8°. This salt is stirred for 1 h with 2 g of sodium hydroxide in 50 mL of water, then chloroform is added, and the mixture is stirred for an additional 30 min. The layers are separated, and the aqueous layer is extracted with chloroform. The chloroform layers are washed with water, then dried, and evaporated to give an oil, which solidifies. It weighs 3.38 g (12.0 mmol, 27%) and has $[\alpha]_{578}$ +150.2°. Acidification of the aqueous layers affords 9.46 g of (−)-**1A** (88% recovery).

Resolution of 4-Methoxy-α-phenylbenzeneethanamine (17). (a) A mixture of 12.5 g of impure amine **17** (55.1 mmol, if pure), 14.5 g of (+)-**9A** (46.6 mmol), and 105 mL of methanol is heated to reflux (part of the product already precipitated) and then allowed to stir at room temperature for 60 h. There is obtained 8.14 g (15.1 mmol, 32%) of the salt with $[\alpha]_{578}$ +76.9°. This salt is stirred for 16 h with 150 mL of 1 N sodium hydroxide solution, and 50 mL of chloroform is added to the suspension,

(21) Kralt, T.; Haeck, H. H.; Peperkamp, H. A. *Recl. Trav. Chim. Pays-Bas* **1966**, *85*, 607.

(22) Ten Hoeve, W.; Wynberg, H. Patent pending (to Océ-Andeno, Venlo, The Netherlands).

which is stirred for another 30 min and then filtered to remove the insoluble sodium salt of the phosphoric acid. The layers are separated, and the aqueous layer is extracted with 50 mL of chloroform. The organic layers are washed with water and then dried and evaporated, and the residue is purified via Kugelrohr distillation [135 °C (0.03 mmHg)] to give 3.05 of amine **17** with $[\alpha]_{578}$ +64.3° (*c* 1.07, CH_3OH).

(b) A mixture of 15.5 g of impure amine **17** (68.3 mmol, if pure), 16.8 g of (−)-**2A** (61.8 mmol), 50 mL of 96% ethanol, and 10 mL of water is heated to solution. After the solution is cooled to room temperature and stirred overnight, there is obtained 7.92 g of the salt (15.9 mmol, 26%) with $[\alpha]_{578}$ −86.3°. This salt is stirred for 5 h with 4.0 g of sodium hydroxide in 100 mL of water, the solution is extracted with 2 × 50 mL of chloroform, the organic layer is washed with 50 mL of water, then dried, and evaporated, and the residue is purified via Kugelrohr distillation to give 3.38 g of amine **17** (14.9 mmol, 24%) with $[\alpha]_{578}$ −63.8° (*c* 1.11, CH_3OH).

Resolution of (*p*-Hydroxyphenyl)glycine. (a) A mixture of 4.19 g of (*p*-hydroxyphenyl)glycine (25.1 mmol), 6.83 g of (+)-**2A** (25.1 mmol), 80 mL of 96% ethanol, and 60 mL of water is warmed until clear. After the solution is stirred for 1 h and stands overnight at room temperature there is obtained 4.36 g of the salt (9.9 mmol, 40%) with $[\alpha]_{578}$ +103.5°. Part of this salt (3.86 g, 8.8 mmol) is stirred for 3 h with 4 mL of concentrated hydrochloric acid and 21 mL of water. The suspension is filtered, the phosphoric acid is washed with water, and the filtrate is neutralized with sodium hydroxide solution. After addition of some ethanol the amino acid precipitated. The yield was 0.52 g with $[a]_D$ +157.8° (*c* 1.01, 1 N HCl). From the filtrate, after partial evaporation, there was obtained another 0.40 g of amino acid (total yield, 0.92 g, 5.5 mmol, 25%).

(b) A mixture of 4.19 g of (*p*-hydroxyphenyl)glycine (25.1 mmol), 6.94 g of (+)-**7A** (25.1 mmol), 60 mL of 96% ethanol, and 55 mL of water is heated to give a solution. After the solution is stirred for 1 h and stands overnight at room temperature, there is obtained 4.18 g of the salt (9.4 mmol, 38%) with $[\alpha]_{578}$ +94.6°. Part of this salt (3.68 g, 8.3 mmol) is hydrolyzed to the amino acid as described above to give a first crop of 0.54 g with $[\alpha]_D$ +156° and a second crop of 0.57 g with $[\alpha]_D$ +158° (*c* 1.03, 1 N HCl) for a total yield of 1.11 g of (*p*-hydroxyphenyl)glycine (6.65 mmol, 30%).

Resolution of Phenylalanine. A mixture of 8.80 g of (−)-**7A** (31.8 mmol), 5.25 g of phenylalanine (31.8 mmol), and 60 mL of water is dissolved in 25 mL of absolute ethanol by warming. After the mixture is stirred for 6 h at room temperature there is obtained 6.03 g of the salt (13.7 mmol, 43%) with $[\alpha]_{578}$ −26.6°. This product is stirred for 7 h with 70 mL of 1 N hydrochloric acid, the phosphoric acid is filtered off and washed with water (to give 3.60 g, 13.0 mmol, of **7A**, i.e., a 95% recovery of the phosphoric acid), the filtrates are evaporated, and the residue is dissolved in 10 mL of water and 5 mL of ethanol. After neutralization with a sodium hydroxide solution there is obtained 1.13 g of phenylalanine with $[\alpha]_{578}$ +34.2° (*c* 1.96, H_2O). From the filtrate there could be obtained an additional 0.77 g of phenylalanine with $[\alpha]_{578}$ +32.8° after purification over a Dowex-H^+ column. The total yield is 1.90 g (11.5 mmol, 36%).

Resolution of Methionine. A mixture of 13.83 g of (+)-**7A** (50.0 mmol), 7.46 g of methionine (50.0 mmol), and 70 mL of 96% ethanol is dissolved in 35 mL of water. After the mixture is stirred for 5 h at room temperature there is obtained 5.46 g of the salt (12.8 mmol, 26%) with $[\alpha]_{578}$ +33.3°. The salt is stirred for 4 h with 6 mL of concentrated hydrochloric acid and 45 mL of water, the phosphoric acid is filtered off and washed with water to give 3.42 g of the phosphoric acid (96% recovery), and the filtrates are evaporated. The residue is purified over a Dowex-H^+ column to give 1.60 g of methionine (10.7 mmol, 21%) with $[\alpha]_{578}$ +21.8° (*c* 0.8, 0.2 N HCl).

2-Chloro-5,5-dimethyl-4-phenyl-1,3,2-dioxaphosphorinane 2-Oxide (20). To a suspension of 24.2 g of (−)-**1A** (0.100 mol) in 150 mL of dichloromethane is added 24.5 g of phosphorus pentachloride (0.118 mmol) over a 5-min period. The resulting solution is stirred for 2.5 h and then evaporated. Ether is added to the residue, the solution is filtered to remove a small amount of phosphorus pentachloride, and the filtrate is stored for 3 days at −15 °C. This gives 5.21 g of the pure acid chloride. From the filtrate another 1.17 g can be obtained, for a total yield of 6.38 g (24.5 mmol, 24%) with $[\alpha]_{578}$ −82.4° and mp 162–164.5 °C. The filtrate is evaporated, and to the residue (probably a mixture of pyrophosphates) is added 16 g of sodium hydroxide in 150 mL of water. An exothermic reaction takes place, resulting in a solution. After the mixture is cool, concentrated hydrochloric acid is added to precipitate the phosphoric acid. After washing and drying there is recovered 14.5 g (59.8 mmol, 60%) of (−)-**1A**. The racemic acid chloride **20** is readily obtained by addition of ether to the crude product from the reaction of diol **1B** and phosphorus oxychloride; it has mp 127.5–129.5 °C: ^1H NMR 0.85 (s, 3 H), 1.1 (s, 3 H), 3.6–4.4 (m), 4.3 (s, 2 H), 5.25 (d, J = 3 Hz, 1 H), 7.25 (s, 5 H). Anal. Calcd for $C_{11}H_{14}ClO_3P$: C, 50.68; H, 5.41; Cl, 13.60; P, 11.88. Found: C, 50.92; H, 5.40; Cl, 13.52; P, 11.92.

Relevant X-ray crystallographic data for the salt from D-(−)-(*p*-hydroxyphenyl)glycine and (−)-7A: $C_{11}H_{14}ClO_4P \cdot C_8H_9NO_3$, M = 443.8, orthorhombic, a = 7.039 (1) Å, b = 10.174 (1) Å, c = 29.645 (4) Å, D_c = 1.388 g/cm^3, V = 2123.0 Å^3, λ = 0.7107 Å, μ = 2.90 cm^{-1}, F(ooo) = 928, space group $P2_12_12_1$, Z = 4, No. 19; Nonius CAD4SDP23M diffractometer, interfaced to a PDP-11/23 instrument, graphite monochromated Mo Kα radiation, ω–2θ scan, 1° ≤ θ ≤ 28°, 2925 unique reflections, 2455 reflections with $I \geq 3\sigma(I)$, 25 reflections with 10° ≤ θ ≤ 12° used to refine unit cell parameters, crystal dimensions 0.50 × 0.50 × 0.20 mm. The structure was solved by direct methods and was based on the known absolute configuration of (−)-(*p*-hydroxyphenyl)glycine. Full-matrix least squares of F converged to a final R = 0.067 and R_w = 0.090 (W = 1), respectively, for the non-H atoms with anisotropic temperature factors. All computations were performed using CAD4SDP programs. Relevant bond distances (Å): Cl–C19, 1.768 (9); C19–C18, 1.339 (11); C19–C14, 1.412 (9); C18–C17, 1.39 (2); C17–C16, 1.34 (2); C16–C15, 1.452 (11); C15–C14, 1.394 (10); C14–C11, 1.519 (7); C13–C10, 1.553 (8); C12–C10, 1.524 (8); C11–C10, 1.532 (7); C11–O6, 1.470 (6); C10–C9, 1.542 (7); C9–O7, 1.469 (7); O6–P, 1.592 (4); P–O7, 1.608 (4); P–O5, 1.492 (4); P–O4, 1.500 (4). Relevant bond angles (deg): C14–C11–C10, 114.8 (5); C14–C11–O6, 106.0 (4); C10–C11–O6, 108.9 (4); C11–C10–C9, 107.0 (4); C10–C9–O7, 111.0 (4); C11–O6–P, 116.8 (3); O6–P–O7, 102.6 (2); O6–P–O5, 111.8 (2); O6–P–O4, 107.1 (2); O7–P–O5, 110.1 (2); O7–P–O4, 107.6 (2); O5–P–O4, 116.7 (2); C9–O7–P, 114.6 (3). Interatomic bond distances (Å): O3–O4, 4.156; O3–O5, 2.568; O2–O4, 3.233; O2–O5, 3.432; N–O4, 2.774; N–O5 3.251. Full details of the X-ray data are available from F. van Bolhuis, Department of Chemical Physics, University of Groningen, Nijenborgh 16, The Netherlands.

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