# Solvent effect in NMR enantiomeric analysis using (*S*)-1,1′-binaphthyl-2,2′-diol as a chiral solvating agent

*O. V. Mikhalev,* O. R. Malyshev, M. G. Vinogradov, G. V. Chel'tsova-Bebutova, and A. V. Ignatenko*

*N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 47 Leninsky prosp., 117913 Moscow, Russian Federation. Fax: +7 (095) 135 5328*

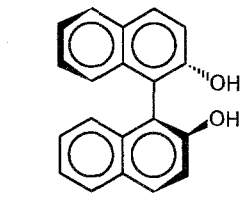
The determination of the enantiomeric composition of chiral compounds by $^{1}H$, $^{13}C$, and $^{31}P$ NMR spectroscopy in the presence of (*S*)-1,1′-binaphthyl-2,2′-diol demonstrates that the enantioselectivity of the method increases when the polarity of a solvent decreases as follows: $CD_3OD—D_2O$ (4 : 1) < $CD_3OD$ < $CDCl_3$ < $CDCl_3—CCl_4$ (1 : 1) < $C_6D_6$. The effect is caused by increase in stability of solvating agent—substrate complexes formed through the hydrogen bonds. Pantolactone, esters of substituted cyclopropanecarboxylic acids, amino alcohol propranolol, and 2,2′-bis(diphenylphosphinyl)-1,1′-binaphthyl were used as the substrates.

**Key words:** (*S*)-1,1′-binaphthyl-2,2′-diol, chiral solvating agent; pantolactone, cyclopropanecarboxylic acids, propranolol, 2,2′-bis(diphenylphosphinyl)-1,1′-binaphthyl, enantiomeric composition; $^{1}H$, $^{13}C$, $^{31}P$ NMR spectra.

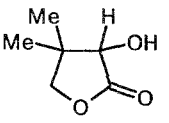
Progress in asymmetric synthesis and catalysis requires adequate development of analytical methods for fast and reliable determination of the enantiomeric composition of compounds of different classes. NMR spectroscopy is among the most widely used methods of enantiomeric analysis. For this purpose, a chiral compound is transformed into a diastereomeric derivative, *e.g.*, an ester or an amide of Mosher acid,[1,2] or the analysis is performed in the presence of chiral lanthanide shift reagents[1] or chiral solvating agents (CSA).[1] The latter make it possible to obtain the spectra without line broadening, which is observed in the presence of paramagnetic complexes of lanthanides.

(*S*)-1,1′-Binaphthyl-2,2′-diol ((*S*)-BINOL) is of great interest. It was used[3—5] for analysis of amines, sulfoxides, and amino alcohols in $CDCl_3$ by $^{1}H$ NMR method. Addition of (*S*)-BINOL causes significant differentiation of the chemical shifts of (*R*)- and (*S*)-enantiomers due to high magnetic anisotropy of the naphthyl nuclei. The absence of its own signals in the $^{1}H$ NMR spectra below 7.0 ppm except the narrow singlet of the OH group at 5.2—5.6 ppm (depending on the solvent and the concentration of CSA) and its rather high solubility in low-polar media are the advantages of this reagent. Being a weak acid, (*S*)-BINOL effectively solvates bases (amines, phosphine oxides, *etc.*) and also compounds capable of forming intermolecular hydrogen bonds (alcohols, esters, lactones).

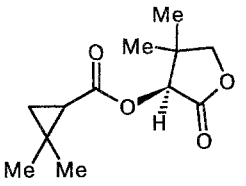
In this paper, experimental data that characterize (*S*)-BINOL as the universal CSA for determination of the enantiomeric composition of the above classes of organic compounds by $^{1}H$, $^{13}C$, $^{31}P$ NMR methods are



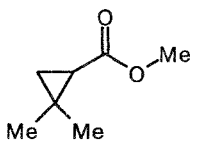

(*S*)-BINOL



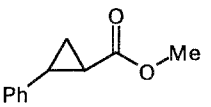

1



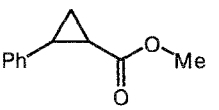

2



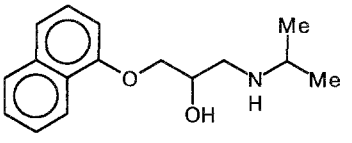

3



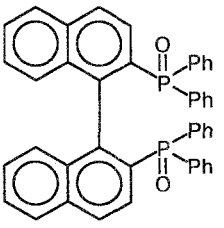

4




5




6




7

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 5, pp. 900—904, May, 1995.

1066-5285/95/4405-0873 $12.50 

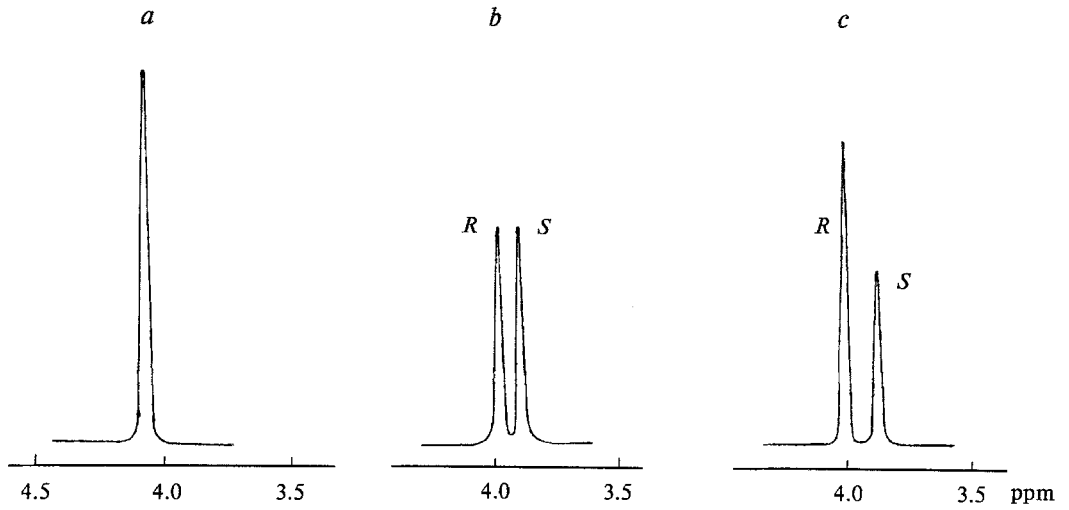



**Fig. 1.** Fragments of $^1$H NMR spectrum of pantolactone (**1**) in $C_6D_6$ in the absence of CSA (*a*); (*RS*)-**1** in the presence of (*S*)-BINOL at BINOL/**1** = 0.5 : 1 molar ratio (*b*); (*R*)-**1**, *ee* 28 %, the same conditions (*c*).

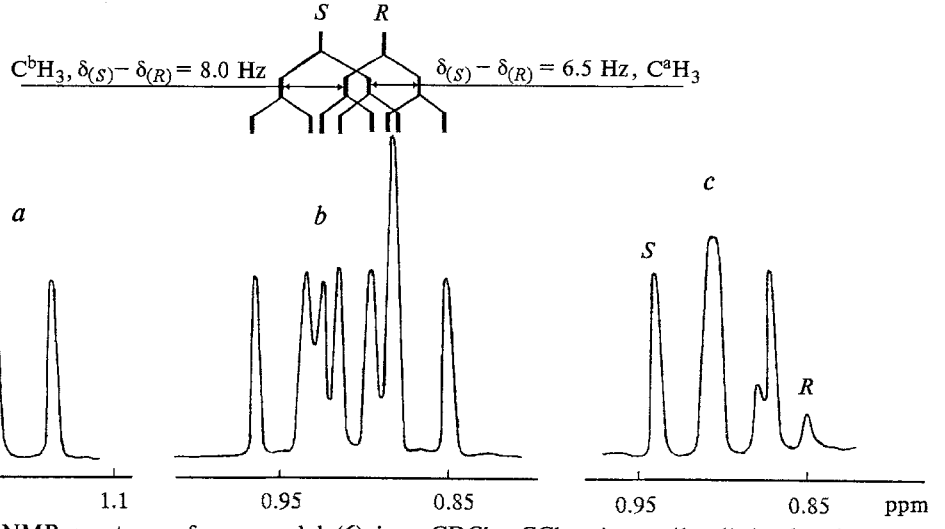



**Fig. 2.** Fragments of $^1$H NMR spectrum of propranolol (**6**) in a $CDCl_3$—$CCl_4$ mixture (1 : 1) in the absence of CSA (*a*); (*RS*)-**6** in the presence of (*S*)-BINOL at BINOL/**6** = 2 : 1 molar ratio (*b*); (*S*)-**6**, *ee* 70 %, the same conditions (*c*).

presented. Practically important compounds, *viz.*, pantolactone (**1**), which is an intermediate in the production of vitamin $B_3$, esters of cyclopropanecarboxylic acids (**2**—**5**), which are intermediates in the synthesis of some insecticides and drugs, propranolol (**6**), which is a β-blocker used in cardiology, and 2,2′-bis(diphenylphosphinyl)-1,1′-binaphthyl (**7**) (BINAPO), which is a precursor of the chiral ligand BINAP that is widely used in asymmetric catalysis, were chosen as substrates for analysis. To assign signals in the NMR spectra of diastereomeric complexes of (*R*)- or (*S*)-enantiomers of these compounds with (*S*)-BINOL, samples of substrates **1**—**7** enriched with one enantiomer (or diastereomer in the case of esters **2**, **4** and **5**) of the known configuration were used.

The data in Table 1 demonstrate the splitting of singlets of the protons of the CH group in compounds **1** and **2** and singlets or doublets of the Me groups of compounds **1**, **3**—**6**. The most pronounced effect was observed on addition of (*S*)-BINOL to pantolactone **1**. In this case, the difference in chemical shifts of the protons of the CH group of (*R*)- and (*S*)-enantiomers is rather high ($\Delta\delta$ = 14 Hz) for effective determination of the enantiomeric purity of pantolactone (Fig. 1).

Enantiomeric composition of the parent cyclopropanecarboxylic acids can be determined by using the $^1$H NMR spectra of acylated pantolactone derivatives with (*S*)-BINOL. In the absence of CSA, the chemical shifts $\delta$ $^1$H of the CH—O fragment of the lactone ring of both diastereomers of ester **2** coincide. Compound **2** was prepared by acylation of (*S*)-pantolactone with (*R**,*S**)-dimethylcyclopropanecarbonyl chloride. Addition of (*S*)-BINOL to ester **2** causes splitting of the $^1$HCO signal: $\Delta\delta$ = 2 Hz in $CDCl_3$ (molar ratio CSA/**2** is 1 : 1).

**Table 1.** Effect of (*S*)-BINOL as CSA on the NMR spectra of substrates **1**—**7** in different solvents[a]

| Substrate | Solvent | Group | CSA/Substrate (mol/mol) | δ $^1$H, $^{13}$C, $^{31}$P | | | Δδ = $(\delta_{(R)} - \delta_{(S)})$/Hz |
|---|---|---|---|---|---|---|---|
| | | | | (*RS*) without CSA | (*R*) + CSA | (*S*) + CSA | |
| **1** | $C_6D_6$ | C $^1$H | 0.5 | 4.05 | 3.94 | 3.87 | 14.0 |
| | | $C^a$ $^1H_3$ | 0.5 | 0.88 | 0.79 | 0.78 | 2.0 |
| | | $C^b$ $^1H_3$ | 0.5 | 0.95 | 0.89 | 0.88 | 2.0 |
| **1** | $CDCl_3$— | C $^1$H | 0.5 | 4.09 | 4.00 | 3.95 | 10.0 |
| | $CCl_4$ | $C^a$ $^1H_3$ | 0.5 | 1.00 | 1.00 | 1.00 | 0.0 |
| | (1 : 1) | $C^b$ $^1H_3$ | 0.5 | 1.16 | 1.15 | 1.14 | 2.0 |
| **1** | $CDCl_3$ | C $^1$H | 1.0 | 4.09 | 4.08 | 4.01 | 14.0 |
| | | $C^a$ $^1H_3$ | 1.0 | 1.00 | 1.00 | 1.00 | 0.0 |
| | | $C^b$ $^1H_3$ | 1.0 | 1.19 | 1.18 | 1.18 | 0.0 |
| **2** | $CDCl_3$ | C $^1$H | 1.0 | 5.40 | 5.38[b] | 5.39[c] | −2.0 |
| | | C $^1$H | 2.3 | 5.40 | 5.27[b] | 5.30[c] | −6.0 |
| **3** | $CDCl_3$ | OC $^1H_3$ | 1.0 | 3.69 | 3.68 | 3.69 | −2.0 |
| **4** | $CDCl_3$— | OC $^1H_3$ | 0.25—0.5 | 3.72 | 3.610[d] | 3.617[e] | −1.4 |
| | $CCl_4$ (1:1) | OC $^1H_3$ | 1.0—2.5 | 3.72 | 3.660[d] | 3.660[e] | 0.0 |
| **5** | $CDCl_3$— | OC $^1H_3$ | 0.25—0.5 | 3.44 | 3.320[d] | 3.325[e] | −1.0 |
| | $CCl_4$ (1 : 1) | OC $^1H_3$ | 1.0—2.5 | 3.44 | 3.380[d] | 3.380[e] | 0.0 |
| **6** | $CDCl_3$— | $C^a$ $^1H_3$ | 2.0 | 1.15 | 0.907 | 0.947 | −8.0 |
| | $CCl_4$ (1 : 1) | $C^b$ $^1H_3$ | 2.0 | 1.15 | 0.858 | 0.890 | −6.5 |
| | | $^{13}C^a$ $H_3$ | 2.0 | 22.45 | 21.96 | 22.21 | −12.5 |
| | | $^{13}C^b$ $H_3$ | 2.0 | 22.45 | 21.70 | 21.90 | −12.0 |
| **6** | $CDCl_3$ | $C^a$ $^1H_3$ | 2.0 | 1.10 | 0.834 | 0.869 | −7.0 |
| | | $C^b$ $^1H_3$ | 2.0 | 1.10 | 0.800 | 0.830 | −6.0 |
| | | $^{13}C^a$ $H_3$ | 2.0 | 22.45 | 21.70 | 21.70 | 0.0 |
| | | $^{13}C^b$ $H_3$ | 2.0 | 22.45 | 22.00 | 22.00 | 0.0 |
| **6** | $CD_3OD$ | $C^a$ $^1H_3$ | 0.5 | 1.077 | 1.077 | 1.077 | 0.0 |
| | | $C^b$ $^1H_3$ | 0.5 | 1.065 | 1.065 | 1.065 | 0.0 |
| | | $^{13}C^a$ $H_3$ | 0.5 | 22.69 | 22.69 | 22.69 | 0.0 |
| | | $^{13}C^b$ $H_3$ | 0.5 | 22.51 | 22.51 | 22.51 | 0.0 |
| **6** | $CD_3OD$ | $C^a$ $^1H_3$ | 2.0 | 1.077 | 1.077 | 1.077 | 0.0 |
| | | $C^b$ $^1H_3$ | 2.0 | 1.077 | 1.063 | 1.065 | −0.4 |
| | | $^{13}C^a$ $H_3$ | 2.0 | 22.69 | 22.40 | 22.40 | 0.0 |
| | | $^{13}C^b$ $H_3$ | 2.0 | 22.51 | 22.28 | 22.28 | 0.0 |
| **6** | $CD_3OD$ | $C^a$ $^1H_3$ | 4.0 | 1.077 | 1.065 | 1.065 | 0.0 |
| | | $C^b$ $^1H_3$ | 4.0 | 1.065 | 1.055 | 1.065 | −2.0 |
| | | $^{13}C^a$ $H_3$ | 4.0 | 22.69 | 22.23 | 22.23 | 0.0 |
| | | $^{13}C^b$ $H_3$ | 4.0 | 22.51 | 22.15 | 22.15 | 0.0 |
| **6** | $CD_3OD$— | $C^a$ $^1H_3$ | 1.0 | 1.10 | 1.020 | 1.020 | 0.0 |
| | $D_2O$ (4 : 1) | $C^b$ $^1H_3$ | 1.0 | 1.08 | 0.992 | 1.000 | −1.6 |
| **7** | $CDCl_3$ | $^{31}$P=O | 1.0 | 29.028 | 30.559 | 30.635 | −2.88 |
| **7** | $C_6D_6$ | $^{31}$P=O | 0.5 | 27.524 | 29.182 | 29.366 | −10.75 |
| **7** | $C_6D_6$ | $^{31}$P=O | 1.0 | 27.524 | 30.257 | 30.703 | −16.80 |
| **7** | $C_6D_6$ | $^{31}$P=O | 2.0 | 27.524 | 31.644 | 32.117 | −17.90 |
| **7** | $C_6D_6$ | $^{31}$P=O | 3.0 | 27.524 | 32.515 | 32.945 | −16.30 |
| **7** | $C_6D_6$ | $^{31}$P=O | 4.0 | 27.524 | 33.720 | 34.117 | −15.04 |

[a] Concentrations of substrates are from 0.04 to 0.20 mol $L^{-1}$; chemical shifts are measured for racemates **1**, **2**, **3**, **6**, **7**; samples enriched with one enantiomer were used to assign the signals in the NMR spectra; esters **4** and **5** were studied as a mixture of diastereomers of the known composition. [b] The value for the (1*R*,3′*S*)-diastereomer. [c] Data for the (1*S*,3′*S*)-diastereomer. [d] The value for the (1*R*)-diastereomer. [e] The value for the (1*S*)-diastereomer.

The enantiomeric composition of cyclopropanecarboxylic acids may also be determined directly from the $^1$H NMR spectra of their methyl esters in the presence of (*S*)-BINOL that can be illustrated by the data on compounds **3**—**5** presented in Table 1. Cyclopropanecarboxylic acids prepared by catalytic chiral

cyclopropanation of alkenes with methyl diazoacetate[6] may be analyzed in the presence of CSA by the NMR method without their isolation from the reaction mixture.

The enantiomeric analysis of propranolol (**6**) in the presence of (*S*)-BINOL may be carried out conveniently using the splitting of doublets of two nonequivalent Me groups. In the limiting case, a duplicated doublet of doublets is observed. However, depending on the concentration of substrate, the CSA/substrate ratio, and the nature of the solvent, overlapping of some signals is possible. Nevertheless, the ratio of enantiomers **6** may be determined quite exactly and reliably from the ratio of the integral intensities of the left border and the right border signals, which are related to the different enantiomers (Fig. 2). The addition of (*S*)-BINOL to amino alcohol **6** in the $CDCl_3$—$CCl_4$ mixture (1 : 1) causes splitting of the signals of the Me and CH groups also in the $^{13}C$ NMR spectrum. The signals of Me groups are practically always split ($\Delta\delta$ = 12 and 12.5 Hz), whereas the signals of CHOH fragments are split only when CSA/**6** > 2 ($\Delta\delta$ = 6 Hz).

(*S*)-BINOL also causes splitting of the singlet of the P=O group in the $^{31}P$ NMR spectrum of racemic diphosphine oxide BINAPO (**7**), possessing axial asymmetry, into two equivalent signals. This fact may be explained by acid-base interaction of the OH and P=O groups of (*S*)-BINOL and substrate **7**. As can be seen from Fig. 3, when the CSA/**7** ratio increases, signals of $^{31}P$=O shift downfield; the difference in chemical shifts of the signals of enantiomers induced by addition of CSA achieves its maximum value when the molar ratio CSA/**7** is 2 : 1 ($\Delta\delta$ = 17.9 Hz) and decreases with increasing excess of CSA (see Table 1). To our knowledge, $^{31}P$ NMR spectroscopy was not applied previously to the determination of the enantiomeric composition of chiral phosphorous-containing compounds in the presence of (*S*)-BINOL.

The data in Table 1 demonstrate that the efficiency of (*S*)-BINOL as a CSA depends strongly on the nature of the solvent. Thus, in the presence of an equimolar amount of CSA, the signals of the protons of both nonequivalent methyl groups in the $^1H$ NMR spectrum of (*RS*)-pantolactone **1** are not split in $CDCl_3$. In a $CDCl_3$—$CCl_4$ mixture (the solubility of the CSA in pure $CCl_4$ is negligible), the singlet of the proton of one methyl group ($C^aH_3$) is split into a doublet, and splitting of the signals of both methyl groups ($C^aH_3$ and $C^bH_3$) is observed in $C_6D_6$.

The choice of a solvent is especially important for compounds that associate slightly with (*S*)-BINOL, such as esters **3**—**5**. For example, the MeO protons of enantiomers **4** and **5** have $\Delta\delta$ = 0 in $CDCl_3$. However, in a $CDCl_3$—$CCl_4$ (1 : 1) mixture, the splitting $\Delta\delta$ is enough for determination of the enantiomeric composition.

A significant solvent effect is also observed for the propranolol—(*S*)-BINOL system. In the presence of a twofold molar excess of CSA, a slight splitting of proton signals of the only $C^aH_3$ group ($\Delta\delta$ = 0.5 Hz) is observed in the $^1H$ NMR spectrum of amino alcohol **6** in $CD_3OD$, whereas with the same excess of CSA in a $CDCl_3$—$CCl_4$ mixture $\Delta\delta$ is 8.0 Hz for $C^aH_3$ and 6.5 Hz for $C^bH_3$. The dependence of the capability of (*S*)-BINOL to induce non-equivalence of chemical shifts of the $^{13}C$ nuclei of the Me groups of (*R*)- and (*S*)-enantiomers of amino alcohol **6** is similar. The signals of both enantiomers coincide in $CD_3OD$, whereas in a $CDCl_3$—$CCl_4$ mixture splitting of the signals of both diastereotopic groups $C^aH_3$ and $C^bH_3$ in compounds **6** is observed ($\Delta\delta$ is 12.5 and 12.0 Hz, respectively).

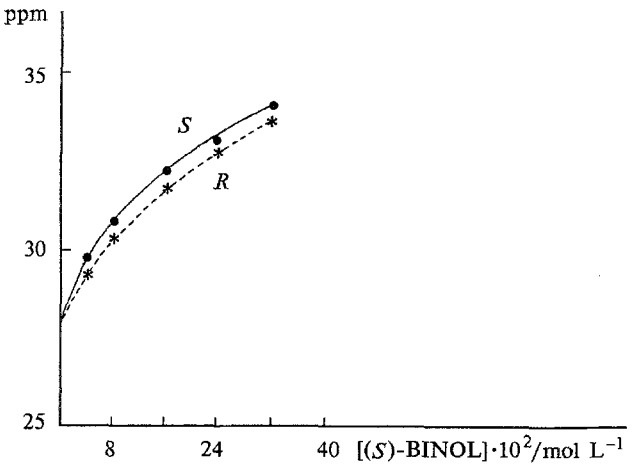



**Fig. 3.** Dependence of chemical shifts of the $^{31}P$=O signals of (*R*)- and (*S*)-enantiomers of diphosphine oxide **7** on the concentration of (*S*)-BINOL in $C_6D_6$.

The difference between the $^{31}P$=O chemical shifts of (*R*)- and (*S*)-enantiomers **7** in the $^{31}P$ NMR spectrum of diphosphine oxide **7** in $CDCl_3$ containing (*S*)-BINOL is 5—6 times lower than that in $C_6D_6$ (see Table 1).

Thus, the capability of (*S*)-BINOL to induce splitting of $^1H$, $^{13}C$, and $^{31}P$ signals in the NMR spectra of compounds **1**—**7** due to stereoselective solvation of one enantiomer (diastereomer) increases with decrease in polarity of the solvent in the following order: $CD_3OD$—$D_2O$ (4 : 1) < $CD_3OD$ < $CDCl_3$ < $CDCl_3$—$CCl_4$ (1 : 1) < $C_6D_6$.

In polar media, the solvation of both the substrate and CSA by the solvent prevents the formation of relatively weak solvate complexes between the substrate and CSA due to hydrogen bonding. This conclusion is confirmed by changes in the $^1H$ NMR spectra of (*S*)-BINOL: the signal of the OH group appears as a narrow singlet, but in the presence of a substrate it transforms into a broad singlet and shifts upfield. Hence, the lower the polarity (and, respectively, the solvation) of the solvent, the more stable is the complex of CSA with the substrate, and, therefore, the stereoselectivity of CSA is higher. Broadening of the OH signals of (*S*)-BINOL in the presence of substrate, the significant

change in the chemical shift and broadening of the OH and NH signals in compounds **1** and **6** during the addition of CSA, downfield shift of the $^{31}P{=}O$ signals (which is characteristic of the protonated P=O group), the mutual increase of solubility of (*S*)-BINOL and the substrate, and the data on the influence of a solvent on the enantioselectivity of (*S*)-BINOL as CSA indicate the formation of hydrogen bonds between CSA and the substrate. Simultaneously, the upfield shifts of the signals in the $^{1}H$ and $^{13}C$ spectra of substrates in the presence of (*S*)-BINOL attest to shielding of the substrate molecule by the planes of the naphthyl nuclei of the CSA molecule.

## Experimental

The NMR spectra were registered with a Bruker AC-200 instrument (200, 50.32, and 81.02 MHz for $^{1}H$, $^{13}C$ and $^{31}P$, respectively) at 20 °C. The $^{13}C\{^{1}H\}$ and $^{31}P\{^{1}H\}$ NMR spectra were obtained under total broad-band proton decoupling ($H_3PO_4$ was used as the external standard). The traces of HCl in $CDCl_3$ and $CCl_4$ were removed by passing the solvents through a layer of freshly calcinated neutral $Al_2O_3$. (*RS*)-1,1′-Binaphthyl-2,2′-diol ((*RS*)-BINOL) was synthesized as reported in Ref. 7. (*S*)-BINOL was obtained by separation of the racemate through diastereomeric derivatives.[8] Pantolactones **1** ((*RS*)- and (*S*)-dihydro-3-hydroxy-4,4-dimethyl-2(3*H*)-furanones) were prepared by recrystallization of the corresponding commercial crude products from $CCl_4$. (*S*)-Dihydro-4,4-dimethyl-2(*H*)-furanone-3-yl-(*R**,*S**)-2′,2′-dimethylcyclopropane-1′-carboxylate (**2**) enriched with the (*S*,*S*)-diastereomer was prepared by esterification of (*S*)-pantolactone **1** with (*R**,*S**)-2,2-dimethylcyclopropanecarbonyl chloride enriched with the (*S*)-enantiomer,[9] the reaction being carried out in benzene in the presence of $Et_3N$. Methyl-(*R**,*S**)-2,2-dimethylcyclopropanecarboxylate (**3**) enriched with one enantiomer was synthesized as reported in Ref. 10. Diastereomeric mixtures of methyl-(1*R**,2*S**)-*trans*-2-phenylcyclopropanecarboxylate (**4**) and methyl-(1*R**,2*R**)-*cis*-2-phenylcyclopropanecarboxylate (**5**) enriched with one diastereomer were prepared as reported in Ref. 10. (*RS*)-Propranolol ((*RS*)-**6**) was separated from commercial drug and was purified by recrystallization from a toluene—hexane mixture (1 : 3). (*S*)-Propranolol ((*S*)-**6**) was prepared by separation of diastereomeric salts using (2*R*,3*R*)-dibenzoyltartaric acid.[11] (2*R*,3*R*)-Dibenzoyltartaric acid was synthesized from (2*R*,3*R*)-tartaric acid.[12] (*RS*)-2,2′-Bis(diphenylphosphinyl)-1,1′-binaphthyl ((*RS*)-BINAPO (**7**)) was synthesized as reported in Ref. 13. (*R*)- and (*S*)-BINAPO (**7**) were prepared from (*RS*)-BINAPO by separation of diastereomeric complexes using (2*R*,3*R*)-dibenzoyltartaric acid.[13]

## References


1. *Asymmetric Synthesis.* **1.** *Analytical Methods,* Ed. J. D. Morrison, Academic Press, Inc., New York—London—Paris—San Diego—San Francisco—San Paulo—Tokyo—Toronto, 1983; 1a. D. Parker, *Chem. Rev.*, 1991, **91**, 1441.
2. S. C. Bensen, P. Cai, M. Colon, M. A. Haiza, M. Tokles, and J. Snyder, *J. Org. Chem.*, 1988, **53**, 5335.
3. F. Toda, K. Mori, and J. Okada, *Chem. Lett.*, 1988, 131.
4. F. Toda, K. Mori, and A. Sato, *Bull. Chem. Soc. Jpn.*, 1988, **61**, 4167.
5. F. Toda, R. Toyotaka, and H. Fukuda, *Tetrahedron; Asymmetry*, 1990, **1**, 303.
6. T. Aratani, *Pure Appl. Chem.*, 1985, **57**, 1839.
7. R. Pummerer and A. Rieche, *Ber.*, 1926, 2159.
8. J. Jacques and C. Fouquey, *Tetrahedron Lett.*, 1971, 4617.
9. M. Elliot and N. F. Tanes, Brit. Pat. Appl. 1260847; *Chem. Abstrs.*, 1970, **73**, 55964.
10. P. E. Kriger and J. A. Landgrebe, *J. Org. Chem.*, 1978, **43**, 4447.
11. H. Foken and H. Krause, GDR Pat. 267486; *Chem. Abstrs.*, 1990, **112**, 55280.
12. C. L. Butter and L. H. Cretcher, *J. Am. Chem. Soc.*, 1933, **55**, 2605.
13. H. Takaya, K. Mashima, K. Koyano, and R. Nayori, *J. Org. Chem.*, 1986, **51**, 629.


*Received September 22, 1994;*
*in revised form February 2, 1995*