Asymmetric Synthesis of New Chiral Europium N,N'-Disuccinate Complexes: Shift Reagents for Aqueous Solutions and Application in the Enantiomeric Excess Determination of Amino Acids

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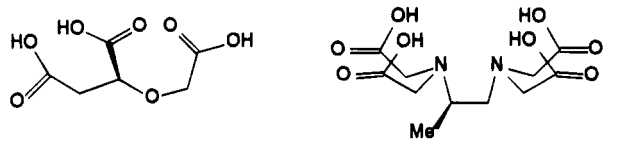
The synthesis of new chiral N,N'-disuccinate ligands (*R,R*)-**8**, (*R,R*)-**9**, and (*S,S*)-**10** from (5*R*)- or (5*S*)-(menthyloxy)-2(5*H*)-furanone is described. These ligands, after complexation with $EuCl_3 \cdot 6H_2O$, are highly suitable as chiral shift reagents for the enantiomeric excess determination of amino acids and α-alkylated amino acids in aqueous solutions. Resolution experiments using various amino acids and their derivatives and a study of the pH dependency of the induced diastereomeric shift differences are included.

Introduction

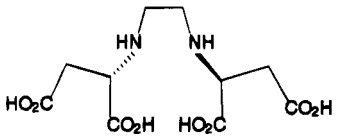
Although many chiral lanthanide shift reagents are known for enantiomeric excess (ee) determinations in *organic* solvents, studies performed on water-soluble chiral shift reagents are rather limited. The direct ee determination of *unprotected amino acids*, in contrast to derivatization methods and subsequent ee determination,[1,2] is an intriguing goal. Since Reuben,[3] in 1980, introduced his self-resolution approach to resolve the enantiomeric nuclei of several α-hydroxy carboxylic acids by means of paramagnetic lanthanide ions only three other systems have been developed for the determination of the enantiomeric excess of unprotected amino acids in water. Van Bekkum and co-workers[4] used a lanthanide derivative of (*S*)-[(carboxymethyl)oxy]succinic acid (**1**) (Scheme 1) to resolve the enantiomeric nuclei of chiral unprotected α-amino acids and α-hydroxy carboxylic acids. Kabuto and Sasaki[5] demonstrated the utility of the Eu^{3+} complex of (*R*)-propylene-1,2-diaminetetraacetate **2** as a powerful chiral shift reagent for aqueous solutions. The most simple and promising chiral water-soluble shift reagent until now is probably the system reported by Kido[6] and co-workers. The ligand, (*S,S*)-ethylenediamine-*N,N'*-disuccinic acid (**3**), is easily prepared by the condensation of two molecules of L-aspartic acid with dibromoethane.[7] Subsequent complexation with $EuCl_3 \cdot 6H_2O$ yields the chiral shift reagent.

The four carboxylic acid and two amine groups in **3** afford an ideal ligand for the lanthanide ion. The original

Scheme 1



1 **2**



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synthesis as described by Major and co-workers,[8] and modified by Neal and Rose,[9] from L-aspartic acid and dibromoethane guarantees the ready availability of the ligand, although structural modifications in the ethylene bridge or acid moieties are not easily introduced.

We therefore developed an alternative route, being the asymmetric synthesis from (5*R*)- or (5*S*)-(menthyloxy)-2(5*H*)-furanone (**4**) (Scheme 2). This route is based on a stereoselective 1,4-addition to two molecules of **4** using suitable diamines, followed by oxidation of the adducts to the desired *N,N'*-disuccinates. This methodology allows structural flexibility in the diamines and affords ligands which, after complexation with Eu^{3+}, are highly suitable as chiral water-soluble shift reagents for the enantiomeric excess determination of unprotected amino acids.

Results and Discussion

Synthesis of Disuccinate Ligands from (5*S*)- or (5*R*)-5-(Menthyloxy)-2(5*H*)-furanone. When (5*S*)-(menthyloxy)-2(5*H*)-furanone (**4**)[10] was treated with 1,2-diaminoethylene, a nearly quantitative double 1,4-addition took place at room temperature (as indicated by ^1H NMR) using CH_2Cl_2 or DMF as solvent, affording the enantiomerically pure 1,2-ethylene bridged bis(men-

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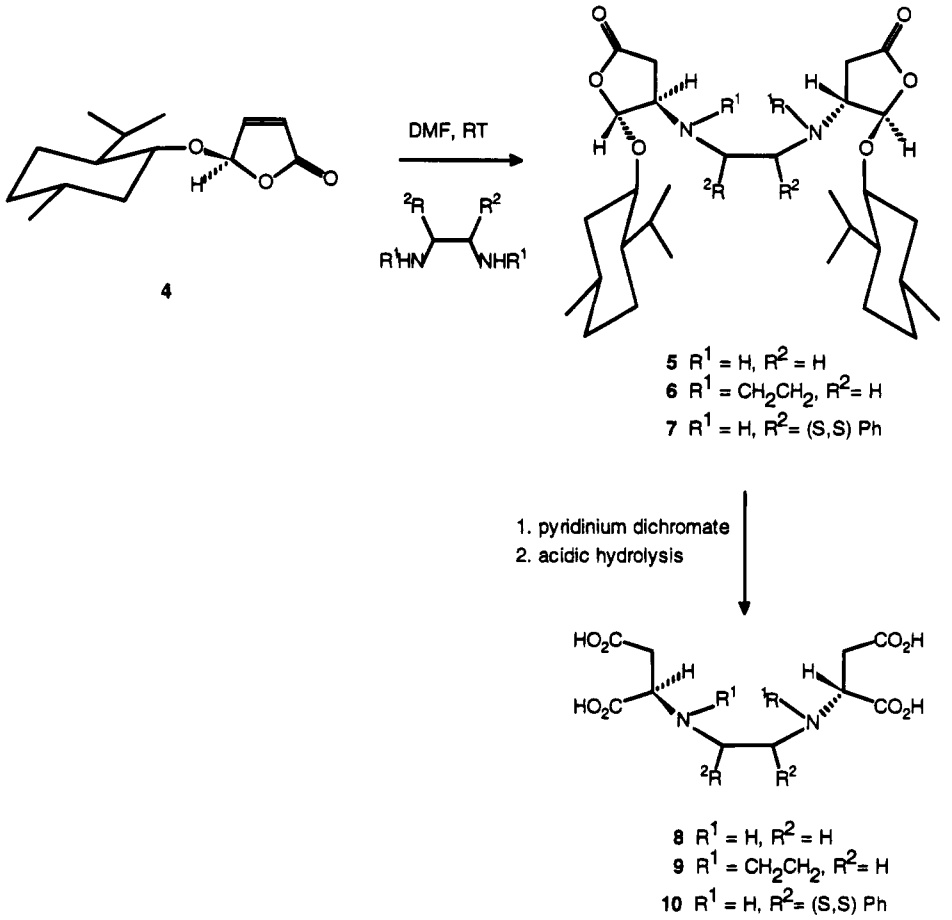
Scheme 2. Synthesis of Ligands 8, 9, and 10 from (5*R*)-5-(Menthyloxy)-2(5*H*)-furanone (4)

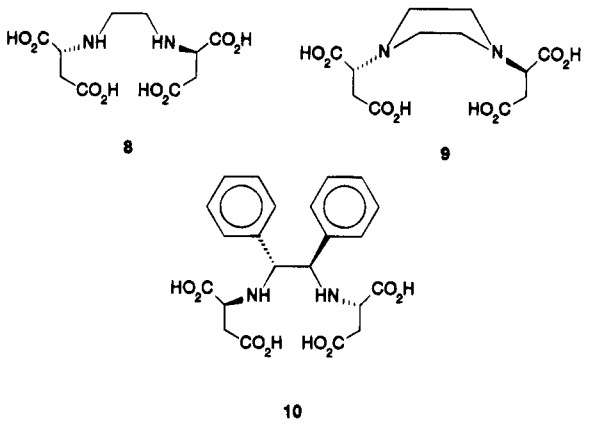


thyloxy)furanone adduct **5** in 71% yield after purification (Scheme 2). Similarly, using piperazine, the piperazine bridged dilactone **6** was obtained in 83% yield. The double 1,4-addition of (*S,S*)-stilbenediamine to (5*R*)-**4** proceeded more slowly, and the reaction is best performed without solvent (neat), affording product **7** in moderate yield (34%) after purification. Moreover, it appeared only to be possible to react (*S,S*)-stilbenediamine with (5*R*)-(menthyloxy)-2(5*H*)-furanone, indicating a strong preference for the reaction of one diastereomeric pair of diamine and chiral butenolide.

Based upon the very small coupling constant (^3J < 2.0 Hz, see Experimental Section) of the acetal proton of products **5**, **6**, and **7**, indicating a trans arrangement of the acetal proton and the proton next to the amine moiety,[10,11] we concluded that the addition of the amines has taken place primarily from the less hindered side of the molecule. Extensive 2D NMR studies performed with (*R,R*)-**5** and (*R,R*)-**6**, using COSY, NOESY, and HetCor techniques, also confirmed the trans arrangement (see supplementary material).

In the reactions described here, some amounts of the *cis–trans* (5–10%) and even *cis–cis* (5%) addition products were formed, indicating that these diamine 1,4-additions were not completely stereoselective, in contrast to previous observations in the monoamine additions to butenolides.[12] Surprisingly, no traces of mono 1,4-adducts were found. Careful crystallization from ethanol afforded the products **5**–**7** as single enantiomers. Subsequent oxidation of **5**, **6**, and **7** using pyridinium dichromate in DMF or acetone followed by basic workup afforded the tetraacids **8**, **9**, and **10**, respectively, in moderate yield after slow crystallization from dilute aqueous HCl (Scheme 3). The analytical data of the ligand (*S,S*)-**8** obtained via this route appeared to be in

Scheme 3



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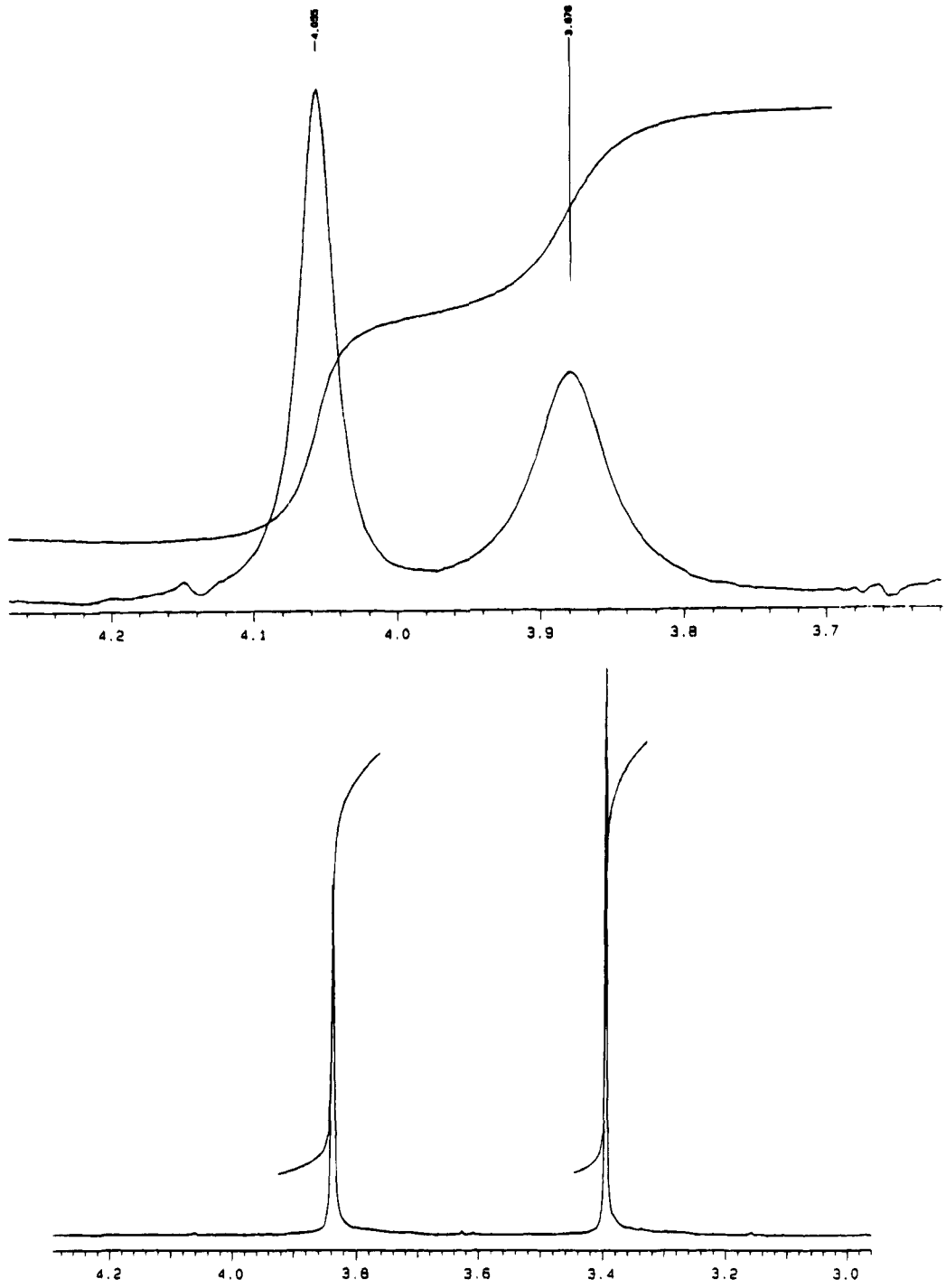

Figure 1. ^{1}H NMR spectra (α-proton) of 0.1 M D,L-phenylglycine in the presence of 0.02 M Eu-(*R,R*)-**8** (upper) and Eu-(*R,R*)-**9** (lower) in D_2O/NaOD.

excellent agreement with the data reported by Kido and co-workers.[6] The ^{1}H and ^{13}C NMR data also clearly indicated that the tetraacids were diastereomerically pure. Attempts to prepare (*R,R*)-**6** and subsequently (*R,R*)-**9** by means of intramolecular dialkylation of (*R,R*)-**5** using 1,2-dibromoethane were not successful.

N,N'-Bridged Disuccinate Europium Complexes as Chiral Shift Reagents. For NMR studies separate solutions were prepared of the amino acids and the Eu(III) complexes of **8**, **9**, and **10** and subsequently combined in the desired ratios. The Eu(III) complexes were prepared by dissolving the desired ligand in D_2O with 4 equiv of NaOD and adding this solution to a D_2O solution of $EuCl_3 \cdot 6H_2O$, according to the method as described by Kido and co-workers.[6] Each amino acid was dissolved in D_2O with an equivalent amount of NaOD, and an appropriate amount of NaCl was added to keep the final concentration at 2 M after combination with the Eu-**8**, Eu-**9**, and Eu-**10** solutions.

The diastereomeric shift nonequivalences of racemic amino acids, obtained using shift reagents Eu-**8** and Eu-**9**, are illustrated for D,L-phenylglycine in Figure 1. The larger upfield shifts of the α-proton of phenylglycine for the L isomer relative to the D isomer upon the addition of the europium complexes of (*R,R*)-**8** or (*R,R*)-**9** are clearly seen. The magnitude of the lanthanide-induced shift was found to increase with the europium complex: phenylglycine ratio, although the line broadening in-

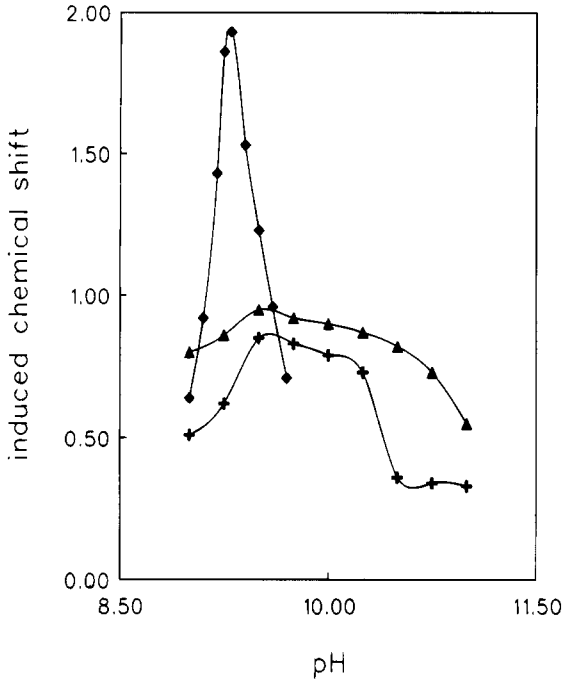

Figure 2. pH dependence of the induced chemical shift ($\Delta\delta$) of D-phenylglycine using the europium complexes of (*R,R*)-**8** (+), (*R,R*)-**9** (▲), and (*S,S*)-**10** (◆).

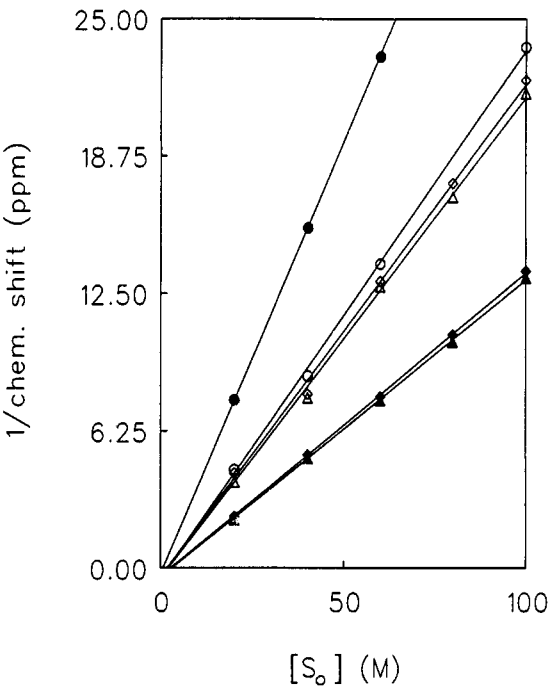

Figure 3. [S_0] versus {1/chemical shift} for L-phenylglycine, Eu-(*R,R*)-**8** (△), Eu-(*R,R*)-**9** (◇), Eu-(*S,S*)-**10** (○); D-phenylglycine, Eu-(*R,R*)-**8** (▲), Eu-(*R,R*)-**9** (◆), Eu-(*S,S*)-**10** (●).

creased also, making a correct determination of the resonance position difficult at higher concentrations. The europium (*S,S*)-**10** complex shows the same kind of behavior, although in this case the D isomers are shifted more upfield relative to the L isomers.

The pH dependence of the induced chemical shift by the Eu complexes was investigated using D,L-phenylglycine as the substrate molecule, at [S_0] = 0.1 and [L] = 0.02 M typically (*vide infra*). Using Eu-(*R,R*)-**8** the resonances of the α-proton of D,L-phenylglycine were shifted upfield, giving the largest shift difference for the L-isomer and a somewhat smaller shift difference for the D-isomer. Both induced chemical shifts ($\Delta\delta$) showed a large dependence upon the pH of the solution (Figure 2) in the pH range 9−11 with a bell shaped profile having a maximum induced chemical shift $\Delta\delta$ at pH 9.5−10. The sharp decreases in $\Delta\delta$ on both the acidic and the basic side probably correspond to oligomerization and hydroxo complex formation, respectively.[13] The Eu-(*R,R*)-**9** complex showed the same type of behavior, also giving a maximum induced chemical shift $\Delta\delta$ at pH 9−10, although the bell-shaped dependence is much less outspoken.

For the Eu-(*S,S*)-**10** system the situation is more complex, primarily due to the limited solubility of this complex at various pH's. The maximum $\Delta\delta$ is located at pH 9.0−9.5, with a sharpe decrease at both sides of this pH optimum. This decrease is probably due to limitations in solubility and not to the factors noted before. This behavior makes it difficult to compare the Eu-**10** complex with the Eu-**8** and the Eu-**9** complex, that do not show such large solubility restrictions. Since all solutions were turbid in the pH range below 9 and above 11, experiments could only be conducted in the pH range 9−11 (actual measurements were made at pH 10), except for the experiments using **10**, for which compound all measurements were performed at pH 9.25.

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The ^{1}H NMR data permitted the determination of the formation constants for the ternary complexes, assuming that only 1:1 Eu ligand:phenylglycine complexes are formed,[14] with equilibrium constant K

$$S_0 = (L_0 + [LS]^2/S_0)(\Delta_b/\Delta\delta) - (L_0 + 1/K) \quad (1)$$

In eq 1, Δ_b is the bound shift of the formed complex and L_0 and S_0 represent the total concentration of lanthanide shift reagent and substrate, respectively. The observed chemical shifts of the nucleus in the presence and absence of shift reagent are given by δ_{obs} and δ_0, respectively. At low lanthanide to substrate ratios,[14] $[LS]^2/S_0$ must be negligible in comparison with L_0 and eq 1 simplifies to eqs 2 and 3

$$S_0 = (L_0\Delta_b/\Delta\delta) - (L_0 + 1/K) \quad (2)$$

$$1/\Delta\delta = \{(S_0 + 1/K)/\Delta_b\}(1/L_0) + 1/\Delta_b \quad (3)$$

A plot of the reciprocal of the induced shift $\Delta\delta$ against the substrate concentration S_0 (at constant lanthanide concentration) affords both the bound shift (slope/L_0) and the association constant ($-1/\{\text{intercept} + L_0\}$). In Figure 3 the plots are given for the three europium ligand systems, at [L_0] = 0.03 M, with D- and L-phenylglycine. For the Eu-(*R,R*)-**8** complex it was found that the data are in good agreement with the data as determined by Kido and co-workers.[6] The association constant for the L isomer (K_L = 5.9) was found to be larger than for the D isomer (K_D = 3.5), while the bound shift for the L isomer (Δ_{bL} = 7.2) was also larger than for the D isomer (Δ_{bD} = 4.4). When Eu-(*R,R*)-**9** was used as shift reagent, these

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Table 1. ΔΔδ Values of Several Racemic Amino Acids Compared for the Chiral Shift Reagents (*R,R*)-Eu-8, (*R,R*)-Eu-9, and (*S,S*)-Eu-10 (α or β Refers to the Nucleus with Greatest Δδ)[a]

substrate	Eu-**8** (ppm)	Eu-**9** (ppm)	Eu-**10** (ppm)
phenylglycine	0.41 (α)	0.51 (α)	1.31 (α)
alanine	0.08 (β)	0.14 (β)	0.31 (β)
serine	0.19 (α)	0.24 (α)	0.43 (α)
threonine	0.27 (α)	0.37 (α)	0.54 (α)
phenylalanine	0.36 (β)	0.33 (β)	1.56 (β)
tyrosine	0.38 (β)	0.34 (β)	1.53 (β)
tryptophan	0.21 (β)	0.17 (β)	0.89 (β)
proline	0.08 (α)	0.16 (β)	0.23 (β)
lysine	0.15 (α)	0.23 (α)	0.48 (α)
histidine	0.25 (β)	0.31 (β)	0.74 (β)
valine	0.18 (α)	0.26 (α)	0.52 (α)
α-Me-PG	0.14 (β)	0.27 (β)	0.89 (β)
α-Me-Phe	0.19 (β)	0.29 (β)	0.64 (β)
α-allyl-PG	0.12 (β)	0.17 (β)	0.93 (β)
α-Me-Val	0.23 (β)	0.25 (β)	0.69 (β)
α-allyl-Ala	0.20 (β)	0.22 (β)	0.99 (β)

[a] Recorded in D_2O at pH 10 (for (*R,R*)-Eu-**8** and (*R,R*)-Eu-**9**) or pH 9.25 (for (*S,S*)-Eu-**10**), $[S_0] = 0.01$ M.

data were not altered in sign, but only in magnitude, yielding $K_L = 6.2$ and $K_D = 3.7$ whereas $\Delta_{bL} = 7.4$ and $\Delta_{bD} = 4.5$.

Due to solubility limitations, complex Eu-(*S,S*)-**10** could not be investigated with the same degree of accuracy as the two other complexes; the association constants and bound shifts were determined to be $K_L = 3.2$, $K_D = 5.4$, $\Delta_{bL} = 7.9$ and $\Delta_{bD} = 13.1$, respectively (±10%).

These data clearly indicate that for the shift reagents Eu-(*R,R*)-**8** and Eu-(*R,R*)-**9** the ternary complexes with the L isomer of phenylglycine are geometrically more favorable, resulting in more stable complexes. For the Eu-(*S,S*)-**10** complex the situation is not clear, the formation constants are comparable with the two other systems, but the observed shift differences are larger. This phenomenon is probably related to the anisotropy effect of the aromatic rings.

The results of resolution experiments using various racemic amino acids using the chiral europium shift reagents Eu-**8**, Eu-**9**, and Eu-**10** are summarized in Table 1. Typically, concentrations of $[S_0] = 0.1$ M and [L] = 0.02−0.03 M at pH 10 or 9.25 (*vide supra*) were used for the measurements.

Sufficient diastereomeric resolution was obtained regardless the structure of the amino acids or amino acid derivatives used, although line broadening sometimes was extensive. Phenylglycine, used as the test substrate, is spectroscopically the most simple chiral amino acid and the signals of the α-proton are readily resolved using one of the three europium complexes, with Eu-(*S,S*)-**10** giving the largest ΔΔδ values. Also using alanine, resolved signals could be obtained with all three europium complexes giving separations for the absorptions of the β-protons. The α-proton signals appeared as quartets, although due to extensive line broadening the exact position was difficult to determine. Again, upon the use of Eu-(*S,S*)-**10** the largest shift differences were obtained. Phenylalanine also yielded the best results when Eu-(*S,S*)-**10** was used, giving the largest shifts for the β-protons of the D-isomer.

When α-alkylated amino acids were used, the line broadening was extensive, so that the resonance position could not always be determined, regardless of the europium ligand system used. It appeared to be possible, however, to use the signals for quantitative ee determination. When primary amino acid amides were used, the line broadening was too extensive to be of use for the determination of the enantiomeric ratios. In these cases the europium ion is probably transferred to the primary amide moiety, giving rise to severe line broadening.

The ratios of several racemic and partially enriched amino acids, as determined with the europium complexes Eu-**8**, Eu-**9**, and Eu-**10**, were compared with the data obtained by the α-chloropropionyl chloride[1] method and the *sec*-butylphosphonate method[2] and appeared to be within the experimental error (2%).[15]

Conclusions

The asymmetric synthesis from enantiomerically pure (menthyloxy)furanone **4** affords chiral tetraacids **8**, **9**, and **10** in reasonable yield. Using this methodology, structural variations are readily introduced in the ligands, as shown for ligands **9** and **10**. This clearly is a major advantage over the current methods described in literature.[4-6]

The in situ prepared europium complexes of the tetraacids **8**, **9**, and **10** appear to be highly suitable as chiral shift reagents for amino acids and α-alkylated amino acids in aqueous solutions. The data obtained using Eu-(*R,R*)-**8** are in excellent agreement with the data as reported by Kido and co-workers.[6] The new Eu-(*R,R*)-**9** and Eu-(*S,S*)-**10** complexes give large and superior diastereomeric shift differences compared to the known Eu-(*R,R*)-**8** system.

Experimental Section

(5*R*)- and (5*S*)-5-(menthyloxy)-2(5*H*)-furanone were prepared according to the method described by Feringa and coworkers.[10] The ^1H (at 300 MHz) and ^{13}C NMR (at 75.43 MHz) spectra were recorded on a Varian VXR-300 spectrometer at 30 °C. The experiments with lanthanide shift reagents were performed using a Varian Gemini-200 spectrometer (at 200 MHz) at 30 °C. All shifts are denoted relative to the solvent used. The pH determinations were done on a Radiometer Copenhagen PHM 82 standard pH meter, using a Corning calomel combination electrode. $EuCl_3{\cdot}6H_2O$ (99.99%) and the amino acids were obtained from Janssen Chimica. Merck silica gel 60 (230−400 mesh ASTM) was used.

Due to solubility limitations and presumably association effects,[16] it was found to be impossible to obtain reproducable accurate rotations and analyses for the tetraacids **8**, **9**, and **10**. Furthermore, the ^1H NMR chemical shifts and coupling constants of **8**, **9**, and **10** are highly pH and concentration dependent.[7]

(4*R*,4'*R*)-1,2-Ethylenediamino-*N,N'*-bis((5*R*)-5-(*l*-menthyloxy)butyrolactone) ((*R,R*)-5). A solution of 1.00 g (4.20 mmol) (5*R*)-5-(menthyloxy)-2(5*H*)-furanone and 0.13 g (2.10 mmol) of ethylenediamine in 10 mL of DMF was stirred for 12 h at room temperature. The solution was taken to dryness, taken up in CH_2Cl_2 (25 mL), and washed 5 times with water (5 mL) and concentrated, after which the residue was purified by column chromatography (silica gel, ethyl acetate−ethanol 95:5) followed by crystallization from ethanol (twice), affording

(15) The accuracy of shift reagents is generally regarded to be a function of several factors, including line broadening, chemical shift difference, and signal to noise ratio. It is generally accepted that when only one peak is observed for enantiotopic nuclei, the presence of the antipode is less than 1.5%, corresponding with an enantiomeric excess of over 97%. For some examples, see: (a) Wenzel, T. J. In *NMR Shift Reagents*; CRC Press: Boca Raton, FL, 1987. (b) Fraser, R. R.; Petit, M. A.; Saunders, J. K. *J. Chem. Soc., Chem. Commun.* **1971**, 1450. (c) Ladner, W. E.; Whitesides, G. M. *J. Am. Chem. Soc.* **1984**, *106*, 7250.

(16) See, for example: (a) Horeau, A. *Tetrahedron Lett.* **1969**, 3121. (b) Lyle, G. G.; Lyle, R. E. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: London, 1983, Vol. 1, p 13.

white needles, which were dried in vacuum at 40 °C for 2 h. Yield 0.80 g (1.49 mmol, 71%). Mp 114–115 °C; $[\alpha]^{20}_D$ = −151.3 (*c* 0.1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 0.80 (d, *J* = 6.84 Hz, 6H), 0.89 (m, 2H), 0.90 (d, *J* = 6.84 Hz, 6H), 0.91 (m, 2H), 0.97 (d, *J* = 6.35 Hz, 6H), 1.07 (m, 2H), 1.25 (m, 2H), 1.43 (m, 2H), 1.49 (s, br, 2H), 1.69 (m, 2H), 1.70 (m, 2H), 2.05 (m, 2H), 2.12 (m, 2H), 2.29 (dd, *J* = 17.58, 2.93 Hz, 2H), 2.76 (s, 4H), 2.87 (dd, *J* = 17.58, 6.84 Hz, 2H), 3.34 (ddd, *J* = 6.84, 2.93, 0.73 Hz, 2H), 3.35 (dt, *J* = 10.74, 3.91 Hz, 2H), 5.44 (d, *J* = 0.73 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 15.59 (CH_3), 20.74 (CH_3), 22.12 (CH_3), 23.12 (CH_2), 25.52 (CH), 31.29 (CH), 34.24 (CH_2), 34.92 (CH_2), 39.70 (CH_2), 46.80 (CH_2), 47.72 (CH), 59.99 (CH), 76.85 (CH), 103.71 (CH), 174.91 (C); HRMS calcd. 536.383, found 536.383. Anal. Calcd. for $C_{30}H_{52}N_2O_6$, C: 67.13, H: 9.76, N: 5.22. Found, C: 67.05, H: 9.76, N: 5.30.

(4*S*,4′*S*)-1,2-Ethylenediamino-*N*,*N*′-bis((5*S*)-5-(*d*-menthyloxy)butyrolactone) ((*S*,*S*)-5): prepared from (5*S*)-5-(menthyloxy)-2(5*H*)-furanone as described for (*R*,*R*)-**5**. Mp 116–118 °C; $[\alpha]^{20}_D$ = +152.6 (*c* 0.1, $CHCl_3$). Further analytical data were found to be identical as described for (*R*,*R*)-**5**.

(4*R*,4′*R*)-1,2-Diaminobisethylene-*N*,*N*,*N*′,*N*′-bis((5*R*)-5-(*l*-menthyloxy)butyrolactone) ((*R*,*R*)-6). A solution of 1.00 g (4.20 mmol) (5*R*)-5-(menthyloxy)-2(5*H*)-furanone and 0.18 g (2.10 mmol) piperazine in DMF (10 mL) was stirred for 1 h at room temperature, after which crystals formed spontaneously. The crystals were filtered off and washed with small amounts of water and briefly dried in vacuum at 40 °C. Recrystallization (twice) from ethanol afforded small white needles. Yield 0.97 g (1.74 mmol, 83%). Mp 152–153 °C; $[\alpha]^{20}_D$ = −173.5 (*c* 0.1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 0.76 (d, *J* = 6.95 Hz, 6H), 0.83 (m, 2H), 0.87 (d, *J* = 6.95 Hz, 6H), 0.91 (m, 2H), 0.94 (d, *J* = 6.22 Hz, 6H), 1.01 (m, 2H), 1.21 (m, 2H), 1.38 (m, 2H), 1.63 (m, 2H), 1.66 (m, 2H), 2.02 (m, 2H), 2.10 (m, 2H), 2.46 (dd, *J* = 17.95, 4.03 Hz, 2H), 2.50 (m, 4H), 2.58 (m, 4H), 2.77 (dd, *J* = 17.95, 8.06 Hz, 2H), 3.16 (ddd, *J* = 8.06, 4.03, 1.83 Hz, 2H), 3.53 (dt, *J* = 10.61, 4.39 Hz, 2H), 5.53 (d, *J* = 1.83 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 15.57 (CH_3), 20.76 (CH_3), 22.17 (CH_3), 23.03 (CH_2), 25.42 (CH), 31.28 (CH), 31.30 (CH_2), 34.20 (CH_2), 39.52 (CH_2), 47.66 (CH), 49.33 (CH_2), 65.87 (CH), 77.02 (CH), 101.26 (CH), 174.60 (C); HRMS calcd. 560.382 (M^+ −2H), found 560.382. Anal. Calcd. for $C_{32}H_{54}N_2O_6$, C: 68.29, H: 9.67, N: 4.98. Found, C: 68.04, H: 9.96, N: 4.99.

(4*S*,4′*S*)-1,2-Diaminobisethylene-*N*,*N*,*N*′,*N*′-bis((5*S*)-5-(*d*-menthyloxy)butyrolactone) ((*S*,*S*)-6): prepared from (5*S*)-5-(menthyloxy)-2(5*H*)-furanone as described for (*R*,*R*)-**6**. Mp 153–154 °C; $[\alpha]^{20}_D$ = +175.0 (*c* 0.1, $CHCl_3$). Further analytical data were found to be identical as described for (*R*,*R*)-**6**.

(4*S*,4′*S*)-1,2-Diaminodiphenylethylene-*N*,*N*′-bis((5*S*)-5-(*d*-menthyloxy)butyrolactone) ((*S*,*S*)-7). A mixture of 1.00 g (4.20 mmol) (5*S*)-5-(menthyloxy)-2(5*H*)-furanone and 0.45 g (2.10 mmol) (−)-stilbenediamine was heated at 120 °C for 48 h. The brown solution was cooled to room temperature and purified by means of column chromatography (silica gel, ethyl acetate-ethanol 95–5) followed by crystallization from ethanol, affording yellow crystalline material. Yield 0.53 g (0.77 mmol, 34%). Mp 94–95 °C; $[\alpha]^{20}_D$ = 99.0 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 0.54 (m, 2H), 0.59 (d, *J* = 6.96 Hz, 6H), 0.66 (m, 2H), 0.71 (d, *J* = 7.37 Hz, 6H), 0.74 (m, 2H), 0.76 (d, *J* = 6.59 Hz, 6H), 0.88 (m, 2H), 0.55–0.98 (s, br, 2H), 1.01 (m, 2H), 1.46 (m, 2H), 1.57 (m, 2H), 1.79 (m, 2H), 2.08 (m, 2H), 2.19 (dd, *J* = 17.94, 1.47 Hz, 2H), 2.66 (dd, *J* = 17.94, 6.96 Hz, 2H), 3.17 (ddd, *J* = 6.96, 1.47, 0.84 Hz, 2H), 3.20 (dt, *J* = 10.62, 5.86 Hz, 2H), 3.53 (s, 2H), 5.00 (d, *J* = 0.84 Hz, 2H), 6.89–6.99 (m, 2H), 7.00–7.21 (m, 8H); ^{13}C NMR ($CDCl_3$): δ 15.39 (CH_3), 20.64 (CH_3), 21.98 (CH_3), 22.89 (CH_2), 25.30 (CH), 31.06 (CH), 34.09 (CH_2), 34.69 (CH_2), 39.07 (CH_2), 47.36 (CH), 59.09 (CH), 67.69 (CH), 76.36 (CH), 103.94 (CH), 127.52 (CH), 127.55 (CH), 128.33 (CH), 140.05 (C), 175.39 (C); HRMS calcd. 344.223, M^+ found 344.223. Anal. Calcd. for $C_{42}H_{60}N_2O_6$, C: 73.22, H: 8.78, N: 4.06. Found C: 73.01, H: 8.74, N: 3.97.

(*R*,*R*)-1,2-Diaminoethylene-*N*,*N*′-disuccinate ((*R*,*R*)-8). A mixture of 0.50 g (0.93 mmol) (*R*,*R*)-**5** and 1.10 g (3.0 mmol) pyridinium dichromate in DMF (25 mL) and H_2O (0.1 mL) was stirred for 24 h at room temperature. The red solution was subsequently acidified to exactly pH 4 (using a 4 N HCl solution) and concentrated to 10 mL. The mixture was taken in 100 mL CH_2Cl_2 and washed five times with a saturated NH_4Cl solution (15 mL), three times with water (15 mL) and concentrated to dryness. The crude material was taken in water (50 mL) containing 0.23 g NaOH (5.75 mmol) and vigorously stirred for 30 min. After this period the mixture was slowly acidified to pH 3.5 with concentrated HCl (to pH 3.0–3.5) with stirring. The precipitated white needles were collected by filtration and the sequence was repeated two more times. The final crop of white needles was washed with a minimum amount of cold water and dried in vacuum at 65 °C for 6 h. Yield 0.07 g (0.24 mmol, 26%). Mp > 250 °C; ^1H NMR (D_2O/NaOD): δ 2.31 (dd, *J* = 24.91, 13.58 Hz, 2H), 2.51 (dd, *J* = 24.91, 7.92 Hz, 2H), 2.78 (d, *J* = 13.60 Hz, 2H), 2.84 (d, *J* = 13.60 Hz, 2H), 3.40 (dd, *J* = 13.58, 7.92 Hz, 2H); ^{13}C NMR (D_2O/NaOD/methanol): δ 42.12 (CH_2), 47.36 (CH_2), 62.15 (CH), 180.37 (C), 182.07 (C); HRMS calcd. 292.091, found 292.090.

(*S*,*S*)-1,2-Diaminoethylene-*N*,*N*′-disuccinate ((*S*,*S*)-8): prepared from (*S*,*S*)-**5** in exactly the same way as described for (*R*,*R*)-**8**. Analytical data were found to be identical as described for (*R*,*R*)-**8**.

(*R*,*R*)-1,2-Diaminobisethylene-*N*,*N*,*N*′,*N*′-disuccinate ((*R*,*R*)-9). A mixture of 0.50 g (0.88 mmol) (*R*,*R*)-**6** and 1.05 g (2.86 mmol) pyridinium dichromate in acetone (25 mL) and H_2O (0.1 mL) was stirred for 24 h at room temperature. The red solution was subsequently acidified to exactly pH 5 (using a 4 N HCl solution) and concentrated to 10 mL. The mixture was taken in 100 mL of CH_2Cl_2 and washed five times with a saturated NH_4Cl solution (15 mL), three times with water (15 mL) and concentrated to dryness. Further workup as described for (R)-**8** afforded white crystalline material. Yield 0.06 g (0.19 mmol, 21%). Mp > 250 °C; ^1H NMR (D_2O/NaOD): δ 2.42 (dd, *J* = 25.52, 14.87 Hz, 2H), 2.48 (dd, *J* = 25.52, 8.77 Hz, 2H), 2.64 (m, 4H), 2.69 (m, 4H), 3.19 (dd, *J* = 14.87, 8.77 Hz, 2H); ^{13}C NMR (D_2O/NaOD/methanol): δ 41.78 (CH_2), 42.04 (CH_2), 46.12 (CH_2), 61.23 (CH), 179.51 (C), 181.34 (C); HRMS calcd. 318.106, found 318.106.

(*S*,*S*)-1,2-Diaminobisethylene-*N*,*N*,*N*′,*N*′-disuccinate ((*S*,*S*)-9): prepared from (*S*,*S*)-**6** in exactly the same way as described for (*R*,*R*)-**9**. Analytical data were found to be identical as described for (*R*,*R*)-**9**.

(*S*,*S*)-((1*S*,2*S*)-Diaminodiphenylethylene)-*N*,*N*′-disuccinate ((*S*,*S*)-10): prepared from (*S*,*S*)-**7** in exactly the same way as described for (*R*,*R*)-**8**. Yellow solid, yield 14%. Mp > 250 °C; ^1H NMR (D_2O/NaOD): δ 2.20 (dd, *J* = 26.41, 14.78 Hz, 2H), 2.46 (dd, *J* = 26.41, 5.89 Hz, 2H), 3.18 (dd, *J* = 14.78, 5.89 Hz, 2H), 3.42 (s, 2H), 6.83–6.89 (m, 2H), 6.92–7.18 (m, 8H); ^{13}C NMR (D_2O/NaOD/methanol): δ 39.12 (CH_2), 58.56 (CH), 101.45 (CH), 126.65 (CH), 126.98 (CH), 127.56 (CH), 138.98 (C), 178.97 (C), 180.56 (C); HRMS calcd. 444.153, found 444.152.

Typical Procedure for the Enantiomeric Excess Determination. The Eu(III) complexes were prepared by dissolving the desired ligand in D_2O with four equivalents of NaOD and adding this solution to a D_2O solution of $EuCl_3{\cdot}6H_2O$, according to the method as described by Kido and co-workers.[6] Each amino acid was dissolved in D_2O with an equivalent amount of NaOD, and an appropriate amount of NaCl was added to keep the final concentration at 2 M after combination with the Eu-**8**, Eu-**9**, and Eu-**10** solutions. The Eu(III) solution was added in small aliquots to the amino acid solution, until the diastereomeric resolution was large enough to ensure adequate quantification.

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Supplementary Material Available: COSY, NOESY, and HetCor spectra of (*R*,*R*)-**5** and (*R*,*R*)-**6** and ^1H and ^{13}C NMR spectra of **8**, **9**, and **10** (16 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.