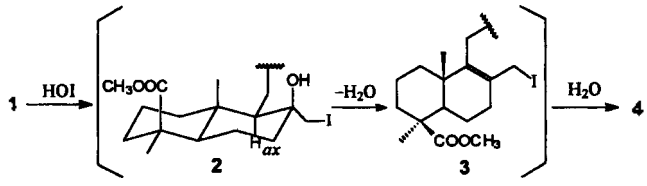

Scheme 2. Conversion of pinusolide (**1**) *via* iodohydrin intermediate (**2**) to 17-hydroxy-8,13-labdadien-16,15-olid-19-oic acid methyl ester (**4**) by treatment with HIO_3 in aqueous acetone.

C-9 (Zaitsev elimination) should yield an allylic iodo intermediate, **3**, which is then readily hydrolyzed to give **4**.[5] The observation that **1** was successfully converted to **4** by the known procedures of iodohydrin formation from olefin, I_2/H_2O[6] and $HIO_3/NaHSO_3$[4] provided a strong support for the proposed reaction pathway shown in Scheme 2. Therefore, treatment with HIO_3 in aqueous acetone provides an efficient alternative method for preparation of iodohydrin from olefin using easily accessible reagents.

Experimental

Melting point was measured on a Mitamura Riken heat block and uncorrected. ^1H NMR and ^{13}CMR spectra were recorded on a Varian Gemini 2000 spectrometer with chemical shifts expressed in δ (ppm) values. IR spectrum was recorded on a Jasco FT/IR-5300 spectrophotometer (KBr pellet). EI mass (EIMS) and high resolution mass (HREIMS) spectra were run on VG TRIO-II GC/MS and HP 5890-JMS AX 505 WA GC-MASS spectrometer, respectively.

17-Hydroxy-8,13-labdadien-16,15-olid-19-oic acid methyl ester (4). To a stirred solution of **1** (3 g, 8.6 mmol) in 80 mL acetone was slowly added HIO_3 (1.52 g, 8.6 mmol) dissolved in 20 mL H_2O at room temperature. The reaction mixture was allowed to react for 2 h, and treated with 150 mL of H_2O. The ether extract was washed with brine and dried over Na_2SO_4. Following evaporation, the organic extract was subjected to silica gel column chromatography ($CHCl_3$: MeOH=100 : 1, R_f=0.2) *to give pure* **4** in white crystals (2.5 g, 80%): mp 134-6 °C (uncorr.); HREIMS [m/z 362.2090; Δ −0.3 mmu $(M)^+$]; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.84 (s, -CH_3), 1.25 (s, -CH_3), 3.67 (s, -OCH_3), 4.11 (1H, d, J=11 Hz, -CH_2OH), 4.24 (1H, d, J=11 Hz, -CH_2OH), 4.83 (2H, dd, J=2.1, 0.8 Hz, lactonyl=$CHCH_2O$-), 7.19 (1H, t, J=0.8 Hz, lactonyl =$CHCH_2O$-); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.6, 16.2, 17.2, 22.4, 24.6, 25.2, 26.6, 33.6, 34.4, 36.5, 40.7, 48.0, 50.0, 60.1, 67.1, 128.7, 131.2, 139.1, 141.2, 171.4, 175.0; IR (KBr) 1694 (lactone, intramolecular hydrogen-bonded), 1761 (ester, C=O), 3542 (sharp, intramolecular hydrogen-bonded allylic OH); GC-MS (EI, m/z, 70 eV, rel. int. %) 362 (M^+, 6.0), 344 (M^+-H_2O, 1.5), 173 (100); Anal. Calcd for $C_{21}H_{30}O_5$: C, 69.59; H, 8.34. Found: C, 69.57; H, 8.42.

General method of conversion of olefins to iodohydrins. In a typical reaction, an olefin (0.3 g) dissolved in 5 mL acetone was added to HIO_3 (2 equiv) solution in water (1 mL). After the mixture was stirred for 12 h at room temperature to complete the reaction, a workup sequence of ether extraction and silica column chromatography afforded the corresponding iodohydrin.

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A New NMR Chiral Solvating Agent Derived from (R)-4-Hydroxyphenylglycine

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Recently we reported the preparation and application of a new chiral stationary phase (CSP **1**) derived from (R)-4-hydroxyphenylglycine for the liquid chromatographic separation of enantiomers.[1] CSP **1** was found to be very excellent in separating the two enantiomers of racemic N-(3,5-dinitrobenzoyl)-α-amino acid amides and esters. The high enantioselectivity of CSP **1** for the two enantiomers of racemic N-(3,5-dinitrobenzoyl)-α-amino acid amides and esters prompted us to extend the use of the chiral selector of CSP **1** as a chiral solvating agent (CSA) for NMR spec-

troscopy. In this study we wish to show that a CSA derived from (R)-4-hydroxyphenylglycine can be utilized in determining the enantiomeric composition of N-(3,5-dinitrobenzoyl)-α-amino acid amides and esters.

CSAs for NMR spectroscopy have been utilized as convenient and practical ones for the determination of enantiomeric composition of chiral compounds by NMR spectroscopy.[2] The two transient diastereomeric adducts formed between the CSA and the two enantiomers of the chiral analyte induce anisochronous NMR resonances and consequently the enantiomeric composition of the chiral analyte can be easily assessed from the NMR spectrum. The convenient and practical nature of CSAs in determining the enantiomeric composition of chiral compounds by NMR spectroscopy has attracted great attention in the fields related to stereochemistry and consequently, various CSAs have been developed.[3] Among others, CSAs utilizing π-π donor acceptor interaction between the CSA and the analyte[4] are directly related to the one we wish to report in this study.

As a suitable CSA, it should show a relatively simple ^{1}H NMR spectrum so as not to be confused with the NMR peaks originated from the analyte and should posses anisotropic groups that give rise to chemical shift nonequivanlence. Based on these, we designed and prepared (R)-**2** as a candidate for a suitable CSA for ^{1}H NMR spectroscopy. The structure of (R)-**2** is quite simple and gives a simple ^{1}H NMR spectrum. In addition, the 4-methoxyphenyl group at the chiral center of (R)-**2** can invoke the enantioselective π-π donor acceptor interaction with the 3,5-dinitrophenyl group of N-(3,5-dinitrobenzoyl)-α-amino acid amides and esters. Consequently, (R)-**2** is expected to be used as a useful CSA.

The ^{1}H NMR experiments for the use of (R)-**2** as a CSA in determining the enantiomeric composition of N-(3,5-dinitrobenzoyl)-α-amino acid amides **3** and esters **4** showed that the chemical shift nonequivalences for the two enantiomers of the analyte are greatest when the stoichiometry of the CSA and the analyte is 2 : 1 at ambient temperature (23±0.5 °C). In addition, the most prominent chemical shift nonequivalences for the two enantiomers of the analyte were observed at the NMR peaks corresponding to the protons of the 3,5-dinitrophenyl ring (denoted a and b in Figure 1) and the N-H proton of the amide group (denoted c in Figure 1). The ^{1}H NMR experimental results for the chemical shift nonequivalences for the protons a, b, and c of analytes **3** and **4** are summarized in Table 1.

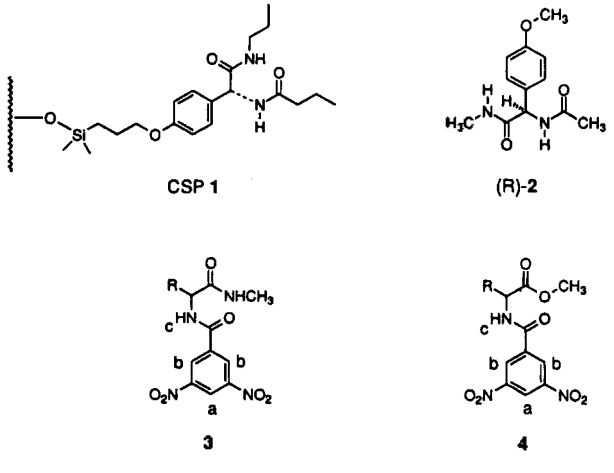

Figure 1. Chemical structures of CSP **1**, (R)-**2**, **3** and **4**. Labels a, b, and c on **3** and **4** correspond to the protons which show ^{1}H NMR chemical shift nonequivalences in the presence of (R)-**2**.

As shown in Table 1, the chemical shift nonequivalences (Δδ) for the N-H proton c of the amide functional group of the analytes are always greater than 0.69 ppm and those (Δδ) for the protons a and b of the 3,5-dinitrophenyl ring of the analytes are always greater than 0.01 ppm. Consequently, any of the chemical shift nonequivalences for the three protons a, b and c can be used in determining the enantiomeric composition of the analytes. For example, the 1H NMR spectrum (Figure 2) observed for the 3 : 1 mixture of (R)- and (S)-N-(3,5-dinitrobenzoyl)phenylalanine methyl ester in the presence of two equivalents of CSA, (R)-**2**, shows that the chemical shift nonequivalences for protons a, b and c are prominent and the heights (or the integrations) of the NMR peaks for protons a, b and c are exactly consistent with the ratio of (R)- and (S)-N-(3,5-dinitrobenzoyl) phenylalanine methyl ester present.

As shown in Table 1 and Figure 2, the chemical shifts for the N-H proton c of the amide functional group of the (S)-enantiomers are observed always greater than those of the (R)-enantiomers. In contrast, the chemical shifts for the protons a and b of the 3,5-dinitrophenyl ring of the (S)-enantiomers are always smaller than those of the (R)-enantiomers. According to the chiral recognition mechanism for resolving N-(3,5-dinitrobenzoyl)-α-amino amides and esters on CSP **1**, the more stable diastereomeric complexes are formed between the CSP and the more retained (S)-enan-

Table 1. ^{1}H NMR chemical shift nonequivalences of the two enantiomers of **3** and **4** induced by (R)-**2**.[a]

Analytes	R	Proton[b]	δ(S) ppm[c]	δ(R) ppm[d]	Δδ [δ(S)-δ(R)]
3	CH_3	a	8.92	9.12	−0.20
		b	8.90	9.05	−0.15
		c	9.25	8.54	0.71
	$(CH_3)_2CH$	a,b	8.94	9.08	−0.14
		c	9.27	8.49	0.78
	$(CH_3)_2CHCH_2$	a,b	8.92	9.06	−0.14
		c	9.20	8.45	0.75
	$C_6H_5CH_2$	a,b	8.86	8.95	−0.09
		c	9.13	8.35	0.78
4	CH_3	a	8.97	9.14	−0.17
		b	8.92	9.02	−0.10
		c	8.52	7.83	0.69
	$(CH_3)_2CH$	a,b	8.97	8.98	−0.01
		c	8.16	7.38	0.78
	$(CH_3)_2CHCH_2$	a	8.93	9.15	−0.22
		b	8.91	9.03	−0.12
		c	8.64	7.73	0.91
	$C_6H_5CH_2$	a	8.97	9.12	−0.15
		b	8.80	8.88	−0.08
		c	8.24	7.48	0.76

[a] See the Experimental part for the experimental conditions. [b] Proton labeled in Figure 1. [c] Chemical shifts of protons a, b and c of (S)-**3** or **4**. [d] Chemical shifts of protons a, b and c of (R)-**3** or **4**.

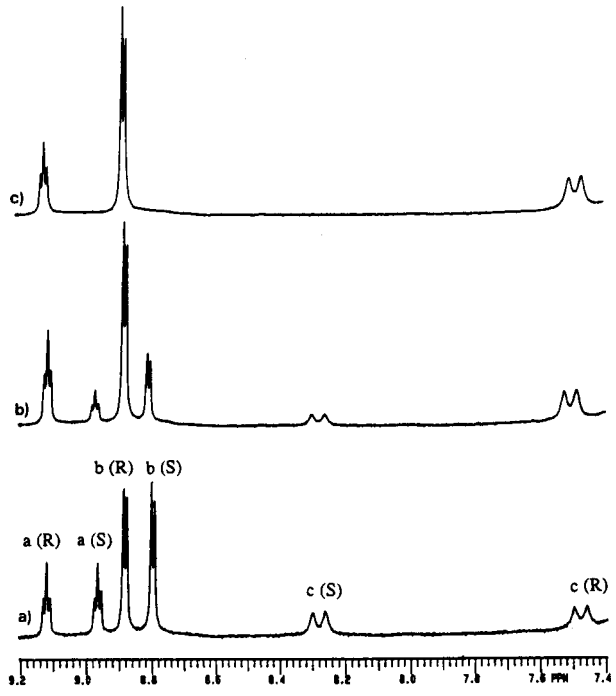

Figure 2. ^{1}H NMR (200 MHz, $CDCl_3$) spectral regions corresponding to the 3,5-dinitrobenzoyl amide proton absorptions of (a) racemic mixture, (b) 3 : 1 mixture of (R)- and (S)-enantiomer and (c) pure (R)-enantiomer of N-(3,5-dinitrobenzoyl)phenylalanine methyl ester (**4**, R=$C_6H_5CH_2$) in the presence of two equivalents of (R)-**2**. Labels a, b and c correspond to protons a, b and c indicated in Figure 1. The relaxation delay between scans was set to 20s. This value was chosen on the basis of the longest relaxation time (T_1=5.3 s) for the proton, a (R), measured by a T_1 experiment.

tiomers utilizing the π-π donor acceptor interaction between the 4-alkoxyphenyl group of the CSP and the 3,5-dinitrophenyl group of the (S)-enantiomers.[1] Similarly, in the ^{1}H NMR experiments, (R)-**2** is also expected to form more stable diastereomeric adducts with the (S)-enantiomers through the face to face π-π donor acceptor interaction between the 4-methoxyphenyl group of (R)-**2** and the 3,5-dinitrophenyl group of the (S)-enantiomers. In this instance, the protons a and b of the 3,5-dinitrophenyl ring of the (S)-enantiomers are expected to experience shielding upon complexation owing to their positioning over the 4-methoxyphenyl ring of (R)-**2** and consequently the resonances of them are shifted to up field. The prominent down field shift of the N-H proton c of the (S)-enantiomers might be rationalized by considering the hydrogen bond between the N-H proton c of the N-(3,5-dinitrobenzoyl) amide functional group of the (S)-enantiomers and any hydrogen bond acceptor of (R)-**2**. However, such a hydrogen bond is not consistent with the chiral recognition mechanism proposed previously for the resolution of **3** and **4** on CSP **1**.[1] Consequently, the N-H proton c of the (S)-enantiomers is rationalized to experience deshielding upon complexation owing to its positioning in the deshielding region of the 4-methoxyphenyl ring of (R)-**2** and consequently, its resonance is shifted to down field.

In summary, we have shown that (R)-**2** can be used as a useful NMR chiral solvating agent in determining the enantiomeric composition of chiral N-(3,5-dinitrobenzoyl)-α-amino amides and esters. The chemical shift nonequivalences for the protons of the 3,5-dinitrophenyl ring and the DNB amide N-H proton of the (R)- and (S)-analytes were large enough to be utilized in the assessment of enantiomeric composition. The large chemical shift nonequivalences were rationalized by the anisotropic effect induced by the 4-methoxyphenyl group of (R)-**2**. However, more precise rationalization should be waited until more experimental results are accumulated.

Experimental

General. All ^{1}H NMR spectra were taken on a Varian Gemini 200 spectrometer (200 MHz). The temperature was maintained at 23±0.5 °C for the duration of ^{1}H NMR experiments. The sample for the ^{1}H NMR experiment was prepared typically by dissolving 7 mg (2.97×10^{-5} mol) of (R)-**2** and 1.48×10^{-5} mol of an analyte in $CDCl_3$ (the total volume of the solution was 0.6 mL). Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane as an internal standard. IR spectra were recorded on a Jasco FT-IR-300E spectrometer. Melting points were taken on a Electrothermal Digital Melting Point Apparatus. Optical rotation was measured on Jasco DIP-1000 polarimeter. Racemic or optically active analytes (**3** and **4**) used in this study were available from previous study.[1]

Preparation of N-methyl amide of (R)-N-acetyl-4-methoxyphenyl-glycine, (R)-2. (R)-**2** was prepared starting from (R)-4-hydroxyphenylglycine via the procedure similar to that for the preparation of the chiral selector of CSP **1**.[1] (R)-N-(tert-Butoxycarbonyl)-4-hydroxyphenylglycine (4.02 g, 15.0 mmole), which was prepared *via* the reaction of (R)-4-hydroxyphenylglycine with di-tert-butyldicarbonate, was dissolved in 100 mL of THF. To the stirred solution were added triethylamine (2.09 mL, 15.1 mmole) and ethylchloroformate (1.43 mL, 15.0 mmole). Into the mixture was introduced methyl amine (CH_3NH_2) gas generated by dropping 40% methyl amine solution onto the excess amount of KOH pellet. After stirring for 1 hr, the whole mixture was concentrated and then dissolved in ethyl acetate. The solution was washed with 2 N HCl and water. The organic solution was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography (ethyl acetate-hexane, 1 : 2, v/v) to afford N-methyl amide of (R)-N-(tert-butoxycarbonyl)-4-hydroxyphenylglycine (3.65 g, 87.3%) as a white crystalline solid. mp 61-62 °C. ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 9H), 2.79 (d, 3H), 5.02 (d, 1H), 5.75-5.79 (m, 1H), 6.06-6.11 (m, 1H), 6.61 (d, 2H), 7.28 (d, 2H). IR (KBr) cm^{-1} 3330, 2978, 1662, 1515. $[\alpha]^{17.8}_D$ − 135.0 (c 0.1 CH_3OH).

N-Methyl amide of (R)-N-(tert-butoxycarbonyl)-4-hydroxyphenylglycine (3.05 g, 10.88 mmole) was dissolved in 150 mL of acetonitrile. To the solution was added K_2CO_3 (3.02 g, 21.77 mmole). After the mixture was heated to reflux for 30 min., methyl iodide (1.56 mL, 25.0 mmole) was added and then the whole mixture was heated to reflux for 6 hrs. The reaction mixture was concentrated and then dissolved in ethyl acetate. The solution was washed with 2 N HCl and water. The organic solution was dried over anhy-

drous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography (ethyl acetate-hexane, 1 : 2, v/v) to afford N-methyl amide of (R)-N-(tert-butoxycarbonyl)-4-methoxyphenylglycine (2.63 g, 82.0%) as a white crystalline solid. mp 164-165 °C. ^{1}H NMR ($CDCl_3$) δ 1.41 (s, 9H), 2.80 (d, 3H), 3.80 (s, 3H), 5.04 (d, 1H), 5.64-5.70 (m, 1H), 5.75-5.79 (m, 1H), 6.86 (d, 2H), 7.28 (d, 2H). IR (KBr) cm^{-1} 3306, 2976, 1700, 1657, 1513. $[\alpha]^{19.1}_D$ − 10.6 (c 0.1 CH_3OH).

N-Methyl amide of (R)-N-(tert-butoxycarbonyl)-4-methoxyphenylglycine (1.28 g, 4.35 mmole) was dissolved in 30 mL of THF. Trifluoroacetic acid (30 mL) was added to the stirred solution and then the mixture was stirred for 3 hrs. The reaction mixture was concentrated. The residue was dissolved in 50 mL of ethyl acetate and then washed with saturated K_2CO_3 solution. The organic solution was dried over anhydrous Na_2SO_4. To the stirred organic solution was added triethylamine (0.81 mL, 4.43 mmole) and acetyl chloride (0.31 mL, 4.43 mmole). The whole mixture was stirred for 5 min., washed with water, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography (ethyl acetate-hexane, 1 : 2, v/v) to afford N-methyl amide of (R)-N-acetyl-4-methyloxyphenylglycine, (R)-**2**, (0.91 g, 88.7%) as a light yellow crystalline solid. The enantiomeric purity of (R)-**2** was greater than 98% ee by HPLC analysis on a commercial chiral column derived from (S)-N-(3,5-dinitrobenzoyl)leucine.[5] mp 225-256 °C. ^{1}H NMR ($CDCl_3$) δ 2.01 (s, 3H), 2.78 (d, 3H), 3.78 (s, 3H), 5.44 (d, 1H), 6.07-6.10 (m, 1H), 6.85 (d, 2H), 6.95 (d, 1H), 7.30 (d, 2H). IR (KBr) cm $^{-1}$ 3288, 3097, 2942, 1685, 1637, 1515. $[\alpha]^{21.8}_D$ − 172.8° (c 0.1, CH_3OH).

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Synthesis of a Polyhydroxylated Pyrrolidine by Regioselective Epoxide Ring-Openning

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There is growing interest in synthetic methodologies towards polyhydroxylated piperidines and pyrrolidines since these compounds have been shown to possess potent inhibitory activities against various glycosidases.[1] These aza sugars have potential therapeutic utility in the treatment of various diseases, such as diabetes,[2] cancer,[3] and viral[4] infections. In view of interest in the structure and enzyme-inhibitory activity relationship, the demand for chemical modification of these compounds has increased. For this reason, many synthetic routes to natural or unnatural aza sugars have been developed over the last few years.

In connection with our project for the preparation of natural or unnatural aza sugars by new methods, here we describe a short and facile synthetic sequence for the synthesis of optically pure polyhydroxylated pyrrolidine **1** by regio- and stereoselective ring-openning of epoxide **7**. Pyrrolidine derivative **1** has methyl instead of hydroxy methyl group on the pyrrolidine ring and these analogs are still a somewhat unexplored class of aza sugars in spite of their interesting glycosidase inhibitory activity. Only one synthesis of isomers of **1** has been so far reported, which was attained *via* thermodynamic process of FDP aldolase catalyzed reaction with an α-substituted β-hydroxyaldehyde.[5]

The mannoate **2**[6] obtained in 87% yield from commercial