Synthesis and Spectral Properties of Optically Active 2-Ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine: Primary Methadone Metabolite

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The synthesis of the optical isomers of 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine is reported. The ^{1}H-nmr analysis suggested that the free bases exist predominantly in an enamine form and the corresponding perchlorate salts in an iminium form. Optical studies showed that the free bases exhibit Cotton effects in the 400-230 nm region and that these Cotton effects are consistent with a fairly rigid enamine structure.

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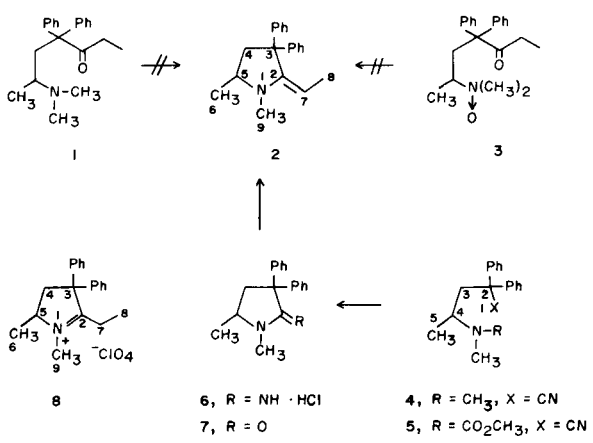
2-Ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP, **2**) (*cf.* Scheme 1) has been identified as the primary metabolite of methadone (**1**) in both humans and rats [1-5]. Subsequent pharmacological studies on *(S)*-(+)-methadone and *(R)*-(−)-methadone [6-9] have underscored a need for pure samples of the EDDP optical isomers. Beckett and co-workers [10,11] have reported the synthesis of the enantiomers of **2** by oxidative *N*-demethylation of methadone (**1**) or reductive *N*-demethylation of methadone *N*-oxide (**3**). The EDDP optical isomers were reported to be unstable but were characterized by chromatographic comparison to the racemic compound and by their ORD properties [11]. The plain ORD curves reported [11] for *(R)*-**2** and *(S)*-**2** seemed unusual since enamines had been reported [12] to show Cotton effects in the region studied. As knowledge of the optical properties of the enantiomers of **2** would facilitate studies of the stereoselective metabolism of methadone, we undertook a study to investigate these properties in more detail.

In order to prepare *(R)*-**2** and *(S)*-**2**, we initially investigated the reported [10,11] one-step conversion of methadone (**1**) or methadone *N*-oxide (**3**) to **2**.This method was of interest not only because it was the sole reported synthesis of optically active **2** but also because it was the only reported synthetic conversion of methadone (**1**) to its primary metabolite [13,14]. However, we found that exposure of methadone (**1**) to the oxidative conditions [10,11] afforded methadone *N*-oxide (**3**) as the only identifiable product whereas exposure of methadone *N*-oxide (**3**) to the reductive conditions [10,11] gave exclusively methadone (**1**). After several unsuccessful attempts to convert either **1** or its *N*-oxide **3** to **2**, we turned to alternative routes.

Scheme I



Pohland and co-workers [3] reported that racemic **2** could be prepared by treating (±)-1,5-dimethyl-3,3-diphenyl-2-pyrrolidone (**7**) with ethyl lithium. We obtained [15] the (±)-pyrrolidone **7** from (±)-4-dimethylamino-2,2-diphenylvaleronitrile (**4**) by treatment with methyl chloroformate, acid hydrolysis of the (±)-carbamate **5**, and subsequent treatment of the (±)-imine hydrochloride **6** with nitrous acid [16]. The (±)-pyrrolidone **7** prepared in this manner was identical in all respects to a sample synthesized using the sequence reported by Gardner and co-workers [17]. Since the methyl chloroformate route involved the use of milder conditions, we preferred it for the preparation of the optically active compounds.

Treatment of the optically active 4-dimethylamino-2,2-diphenylvaleronitriles (**4**) [18] (*cf.* Scheme 1) with excess methyl chloroformate provided the carbamates **5** in 84-88% yield. Subsequent hydrolysis with concentrated hydrochloric acid afforded the cyclic imine hydrochlorides **6**, which in turn were converted to the pyrrolidones **7** using nitrous acid [16]. Higher yields were obtained if the hydrolysis reactions were worked up by basification and extraction, followed by regeneration of the hydrochloride salts **6**. Pure *(R)*-(−)-**7** was obtained in 62% overall yield; *(S)*-(+)-**7** in 38% yield due to difficulty with the isolation of *(S)*-(+)-**6**. The optical isomers of EDDP (**2**) were prepared from the corresponding pyrrolidones **7** and purified as the perchlorate salts **8** using the literature procedure [3] with slight modification.

Since *(R)*-**2** and *(S)*-**2** were prepared by a route different from that reported [10,11], it was necessary to establish

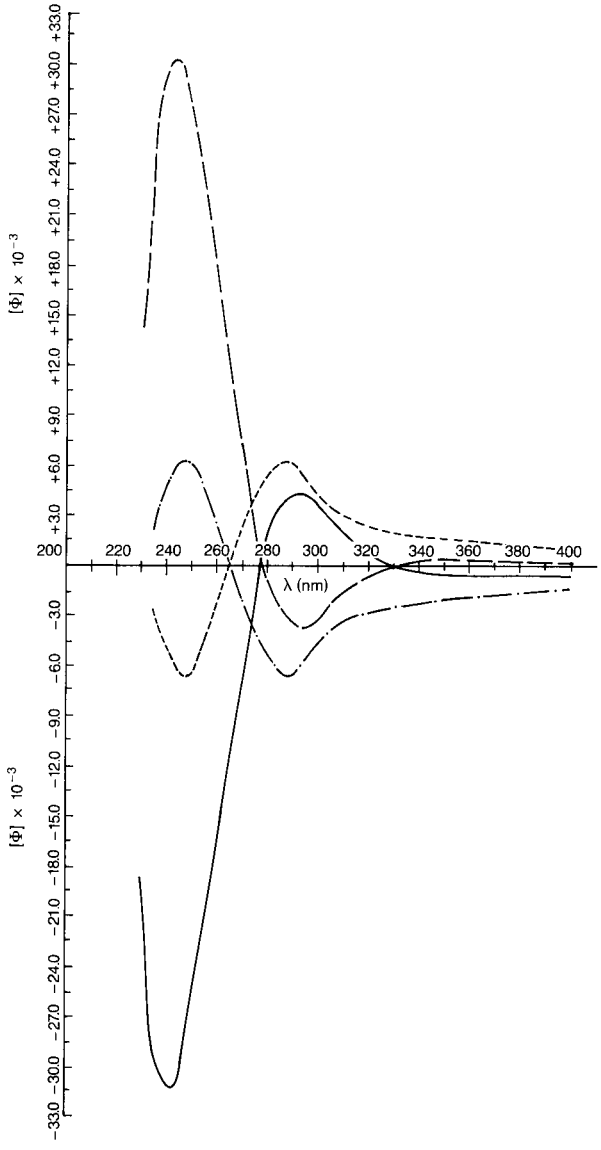


Figure 1. ORD spectra of the 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine isomers and the corresponding perchlorate salts. Legend: — *(R)*-base; - - - *(S)*-base; ···· *(R)*-salt; - • - *(S)*-salt.

firmly the structure of our products. This was accomplished by careful analysis of the ^{1}H-nmr spectra of the perchlorate salts and the corresponding free bases. The ^{1}H-nmr data on the optically active perchlorate salts **8** agreed closely with the data reported [3] for the racemic compound (*cf.* Table 1). Moreover, neutralization of the perchlorate salts **8** with sodium hydroxide provided the optically active EDDP free bases **2** as a 3:2 mixture of *cis* and *trans* isomers. The ^{1}H-nmr spectra of the free bases in deuteriochloroform solution showed doublets at δ 0.93 *(cis)* and 1.70 ppm *(trans)* for the C-8 methyl groups and quartets at δ 4.33 *(cis)* and 3.68 ppm *(trans)* for the C-7 vinyl protons. These patterns were well separated from the other signals and were therefore useful for determining the isomer ratios. In addition, the C-9 methyl groups appeared as singlets at δ 2.62 *(cis)* and 2.79 ppm *(trans)*. These chemical shift values for the free bases were virtually identical to those obtained on the racemic compound by Pohland and co-workers [3].

Since we planned to use absolute ethanol as the solvent for studying the optical properties of the EDDP enantiomers, we also obtained ^{1}H-nmr spectra on the racemic perchlorate salt **8** [19] in ethanol-d_6, methanol-d_4 and methanol-d_3 (*cf.* Table 2). A comparison of the chemical shift data summarized in Table 2 with that reported [3] for deuteriochloroform solution (*cf.* Table 1) indicated that the gross structure of the salt was unchanged in alcohol solution. However, in ethanol-d_6 and methanol-d_4 solution, the multiplet due to the C-7 methylene protons was absent and the δ 0.65 ppm triplet for the C-8 methyl group was collapsed to a singlet. These changes were consistent with the complete exchange of the C-7 methylene protons for deuteriums under the conditions of the ^{1}H-nmr experiments. Due to the absence of an exchangeable deuterium, the normal ^{1}H-nmr patterns for the C-7 and C-8 protons were observed in methanol-d_3 solution (*cf.* Table 2). In contrast to the behavior of the perchlorate salt in alcohol solution, (±)-2-ethyl-1,5-dimethyl-3,3-diphenylpyrrolinium oxalate did not undergo any observable deuterium exchange in deuterium oxide solution [20].

Table 1

^{1}H-NMR Data on the Optically Active Perchlorate Salts [a]

Assignment	(±)-**8** [3]	*(R)*-(+)-**8**	*(S)*-(−)-**8**
C-4 CH_2	2.58, dd J = 6.6, −13.7 3.38, dd J = 8.0, −13.7	2.58, dd J = 6.5, −13.8 3.39, dd J = 8.0, −13.8	2.58, dd J = 6.5, −13.8 3.40, dd J = 8.0, −13.8
C-5 *CH*	4.78, m [b]	4.78, m [c]	4.78, m [c]
C-6 CH_3	1.53, d	1.53, d	1.52, d
C-7 CH_2	2.84, m [d]	2.86, m	2.86, m
C-8 CH_3	0.65, t	0.64, t	0.64, t
C-9 CH_3	3.77, s	3.76, s	3.76, s

[a] The spectra were recorded in deuteriochloroform solution. Chemical shifts are reported in ppm downfield from TMS and J values are reported in hertz. [b] Reported as a sextet [3]. [c] Appeared as a broadened AB quartet. [d] Reported as a complex multiplet [3].

As expected, the ^{1}H-nmr spectrum of the racemic free base in methanol-d_4 showed singlets at δ 0.90 *(cis)* and 1.67 ppm *(trans)* for the C-8 methyl groups and no signals for the corresponding C-7 vinyl protons. Switching to methanol-d_3 again restored the normal patterns, namely quartets at δ 4.35 *(cis)* and 3.67 ppm *(trans)* for the C-7 vinyl protons and doublets at δ 0.90 *(cis)* and 1.66 ppm *(trans)* for

Table 2

Additional ^{1}H-NMR Data on the Racemic Perchlorate Salt

Assignment	CD_3CD_2OD	CD_3OD [a]	CD_3OH [b] [c]
C-4 CH_2	2.64, dd	2.65, dd	2.63, dd
	3.39, dd	3.36, dd	3.34, dd
C-5 CH	4.71, m	4.66, m	——
C-6 CH_3	1.55, d	1.55, d	1.54, d
C-7 CH_2	——	——	2.88, m
C-8 CH_3	0.65, s	0.65, s	0.65, t
C-9 CH_3	3.75, s	3.71, s	3.69, s

[a] Spectrum run after a 3 hour time lapse. A spectrum run immediately after sample preparation showed a multiplet of reduced intensity at δ 2.89 ppm for the C-7 methylene protons and a distorted triplet at δ 0.66 ppm for the C-8 methyl group. [b] Spectrum run with suppression of the hydroxyl signal, which suppression caused the C-5 methine signal to be lost. [c] There was no change between a spectrum run immediately after sample preparation and one run after a 20 hour time lapse.

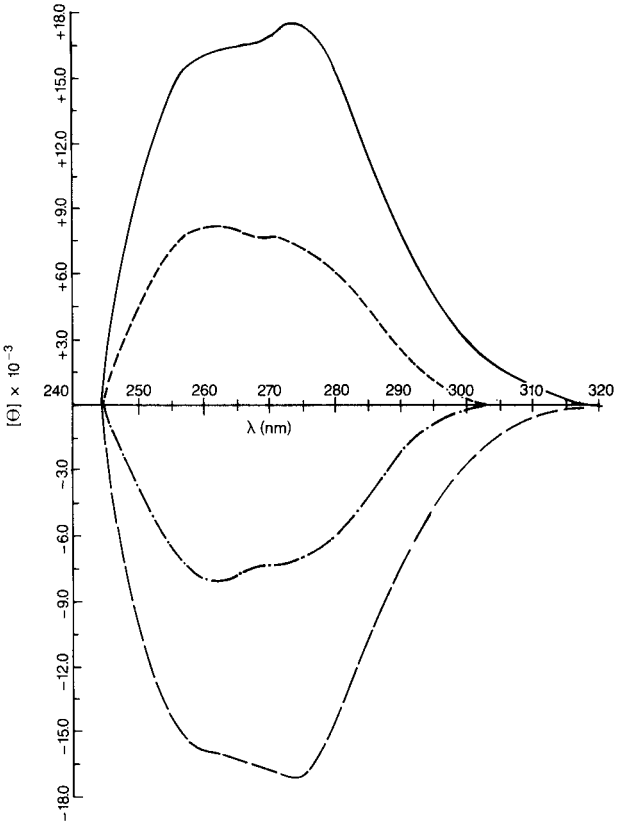


Figure 2. CD spectra of the 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine isomers and the corresponding perchlorate salts. Legend: — *(R)*-base; - - - *(S)*-base; ···· *(R)*-salt; - • - *(S)*-salt.

the C-8 methyl groups. By integration, the ratio of the *cis* and *trans* isomers was still 3:2.

On the basis of the ^{1}H-nmr data, the perchlorate salt **8** existed predominantly in the iminium form (endocyclic double bond) depicted in Scheme 1 in the four solvents examined. Likewise, EDDP free base **2** existed predominantly in the enamine form (exocyclic double bond). However, the facile incorporation of deuterium in ethanol-d_6 and methanol-d_4 indicated that at least in ethanol and methanol solution the perchlorate salt was in equilibrium with a small amount (undetected by ^{1}H-nmr) of the exocyclic double bond tautomer under ambient conditions.

In order to examine the optical properties of the EDDP (**2**) enantiomers in detail, we recorded the ORD and CD spectra of both the free bases **2** and the perchlorate salts **8** in absolute ethanol. The ORD spectra of *(R)*-**2** and *(S)*-**2** from 400-230 nm are shown in Figure 1, and the molar rotations are summarized in Table 3. The curve for *(R)*-**2** shows a negative rotation from 400-330 nm, at which point there is a crossover in rotation. The curve shows a positive Cotton effect with the peak at 293 nm. The trough of this Cotton effect is obscured by a much larger amplitude

Table 3

Molar Rotations of the EDDP Enantiomers [a]

λ max	*(R)*-**2**	*(R)*-**8**	*(S)*-**2**	*(S)*-**8**
400	−0.4	+1.1	+0.4	−1.2
390	−0.4	+1.2	+0.4	−1.2
380	−0.4	+1.3	+0.4	−1.4
370	−0.4	+1.4	+0.4	−1.5
360	−0.4	+1.6	+0.4	−1.7
350	−0.4	+1.7	+0.4	−1.9
340	−0.2	+1.9	+0.3	−2.1
330	0	+2.1	0	−2.3
325	+0.5		−0.2	
320	+0.8	+2.4	−0.5	−2.6
315	+1.3		−0.9	
310	+1.8	+2.9	−1.5	−3.1
305	+2.7	+3.5	−2.3	−3.7
300	+3.6	+4.1	−3.1	−4.5
295	+4.3	+5.1	−3.7	−5.4
290	+4.3	+6.1	−3.5	−6.3
287		+6.3		−6.5
285	+3.6	+6.2	−2.5	−6.3
280	+1.6	+5.2	−0.6	−5.3
277	0		0	
275	−2.3	+3.5	+3.9	−3.6
270	−7.6	+1.9	+8.1	−1.9
265	−10.5	+0.5	+11.2	−0.5
263		0		0
260	−14.6	−1.4	+15.1	+1.4
255	−19.8	−4.5	+20.6	+4.3
250	−25.5	−6.4	+26.3	+6.1
247		−6.6		+6.3
245	−30.6	−6.5	+30.0	+6.1
243	−31.3		+30.4	
240	−31.1	−5.1	+29.9	+4.6
235	−29.3	−2.7	+26.6	+2.1
230	−18.8		+17.2	

[a] Expressed as $[\phi] \times 10^{-3}$, where $[\phi]$ is the molar rotation in deg l/(mol cm). $[\phi]$ is defined by the equation $[\phi] = \alpha M/10\ lc$, where α is the measured rotation in degrees, l is the path length in centimeters, c is the concentration in grams per milliliter, and M is the molecular weight.

lower wavelength negative Cotton effect whose trough is at 243 nm. As expected, the curve of *(S)*-**2** is the mirror image of that of *(R)*-**2**.

We measured the circular dichroism (CD) curves of *(R)*-**2** and *(S)*-**2** from 320-244 nm, and the results are presented in Figure 2 and Table 4. The CD curve of *(R)*-**2** shows a broad, positive Cotton effect with a peak at 274 nm and a shoulder at 265 nm. Similar results were obtained with *(S)*-**2**, but the Cotton effects were all of opposite sign.

The ORD and CD curves of the perchlorate salts **8** of *(R)*-**2** and *(S)*-**2** were also shown in Figures 1 and 2, respectively. The ORD of the perchlorate salt of *(R)*-**2** shows a positive Cotton effect with a peak at 287 nm, a trough at 247 nm and a λ_o 263 nm. However, in contrast to the free base, the larger amplitude lower wavelength negative Cotton effect is absent. In addition, there is no crossover in the long wavelength rotation. The CD curve of *(R)*-(+)-**8** shows a broad band similar to that of the free base; however, the positive maximum is at 262 nm with a shoulder at 270 nm. The magnitudes of the Cotton effects are smaller than those in the CD of the free base. As expected, the ORD and CD curves of *(S)*-(−)-**8** are the mirror images of the curves recorded for *(R)*-(+)-**8**.

Table 4

Molar Ellipticites of the EDDP Enantiomers [a]

λ max	*(R)*-**2**	*(R)*-**8**	*(S)*-**2**	*(S)*-**8**
316	0	0	0	0
312	0.5	0	−0.4	0
308	0.9	0	−0.8	0
304	1.7	0	−1.4	0
300	2.7	0.3	−2.7	−0.2
296	4.5	0.9	−4.1	−0.6
292	6.6	1.8	−6.4	−1.5
288	9.3	3.1	−8.9	−2.9
284	12.1	4.8	−11.6	−4.5
280	15.3	6.2	−14.4	−5.9
276	17.2	7.0	−16.6	−6.8
274	17.5		−17.1	
272	17.4	7.6	−16.9	−7.3
270	17.0	7.7	−16.7	−7.3
268	16.6	7.7	−16.5	−7.4
267		7.7		−7.5
266	16.5	7.9	−16.3	−7.6
265		8.0		−7.8
264	16.5	8.1	−16.2	−8.0
263		8.2		−8.0
262	16.2	8.3	−16.0	−8.1
261		8.2		−8.0
260	16.0	8.1	−15.9	−8.0
258	15.7	8.0	−15.7	−7.7
256	15.3	7.5	−15.0	−7.0
254	13.7		−13.7	
252	11.9	5.5	−11.8	−5.0
250	9.8		−9.6	
248	6.9	2.7	−7.1	−2.7
246	3.6		−4.0	
244	0	0	0	0

[a] Expressed as $[\theta] \times 10^{-3}$, where $[\theta]$ is the molar rotation in deg l/(mol cm). $[\theta]$ is defined by the equation $[\theta] = \psi M/10\ lc$, where ψ is the measured ellipticity in degrees, l is the path length in centimeters, c is the concentratin in grams per milliliter, and M is the molecular weight.

As discussed earlier, the ^{1}H-nmr data suggested that the EDDP free bases **2** exist predominantly in the enamine form while the perchlorate salts **8** exist predominantly in the iminium form. We believe that the Cotton effects observed for the free bases reflect a $\pi \rightarrow \pi^*$ transition in the enamine. Moreover, the amplitudes of the Cotton effects, especially the lower wavelength Cotton effect, suggest a fairly rigid geometry between the exocyclic double bond and one of the nitrogen p orbitals, generating an inherently asymmetric chromophore. A rigid geometry is consistent with the presence of the nitrogen atom in a five-membered ring with restricted rotation along the C-N bond of the enamine. Similar observations were made by Yogev and Mazur [12] in a study of some steroidal enamines and enol ethers. Due to its different geometry and electronic structure, the same Cotton effects are not possible for the iminium chromophore. Indeed the similarities between the ORD and CD curves of the perchlorate salts and those of the free bases may be due to a small amount of the exocyclic double bond tautomer in equilibrium with the iminium form.

In summary we observed that the EDDP optical isomers exhibited Cotton effects in the 400-230 nm region and that their ORD curves were consistent with their cyclic enamine structures. We expect that these findings will facilitate identification of the individual isomers and thus aid future studies of the stereoselective metabolism of methadone.

EXPERIMENTAL

Melting points were taken on a Thomas-Hoover Uni-melt apparatus and are uncorrected. Optical rotations were obtained on a Perkin-Elmer 141 polarimeter; uv spectra on a Cary 14 spectrophotometer. ORD and CD spectra were recorded on a Durrum-Jasco J-20 spectropolarimeter calibrated with a d-10-camphorsulfonic acid standard. The ^{1}H-nmr spectra were run on either a Varian HA-100 or a Bruker 250 MHz instrument. Elemental analyses were performed by Micro-Tech Laboratories, Inc., Skokie, IL.

(R)-(+)-4-(*N*-Carbomethoxy-*N*-methyl)-2,2-diphenylvaleronitrile [*(R)*-(+)-**5**].

A mixture of *(R)*-(−)-**4** [18] (20.0 g, 0.072 mole), sodium bicarbonate (70.0 g, 0.83 mole), and methyl chloroformate (120 g, 1.3 moles) in chloroform (800 ml) was refluxed 44 hours. Additional methyl chloroformate (10 g) was added, and reflux continued 4 hours more, after which time no starting material remained. The mixture was filtered, and the solids were washed with chloroform. The combined filtrate and washings were extracted with 10% hydrochloric acid and with saturated sodium chloride solution, dried (sodium sulfate), and evaporated to give 20.5 g (88%) of the carbamate as a white solid. This material was sufficiently pure for the next reaction.

A 2.00 g sample of the carbamate was flushed through a silica gel column (100 g) using chloroform. Recrystallization of the chromatographically pure carbamate from ethyl ether/petroleum ether gave 1.29 g of

white crystals, mp 98-99°; $[\alpha]_D^{25}$ +26.0° (c 1, 100% ethanol).

Anal. Calcd. for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.57; H, 6.91; N, 8.68.

(S)(−)-4-(*N*-Carbomethoxy-*N*-methyl)-2,2-diphenylvaleronitrile [*(S)*(−)-**5**].

The *(S)*(−)-carbamate was prepared as described above from *(S)*(+)-**4** [18] (20.0 g) in 84% crude yield. Purification of a 2.00 g sample gave 1.41 g of white crystals; mp 98-99°; $[\alpha]_D^{25}$ −26.6° (c 1, 100% ethanol).

Anal. Calcd. for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.56; H, 6.92; N, 8.69.

(R)(−)-2-Imino-1,5-dimethyl-3,3-diphenylpyrrolidine Hydrochloride [*(R)*(−)-**6**].

A solution of crude *(R)*(+)-**5** (12.0 g, 0.037 mole) in concentrated hydrochloric acid (300 ml) was refluxed 42 hours. The mixture was cooled, diluted with water (800 ml), and extracted with ethyl ether (3×). The aqueous layer was basified with concentrated ammonium hydroxide and again extracted with ethyl ether (3×). The second ethyl ether extracts were dried (potassium carbonate) and evaporated to obtain 8.0 g (82%) of the imine base as a white solid. Recrystallization of a 1.60 g sample from ethyl ether/petroleum ether afforded 0.75 g of white needles, mp 117.5-118.5°, $[\alpha]_D^{25}$ −145° (c 1.01, 100% ethanol).

Anal. Calcd. for $C_{18}H_{20}N_2$: C, 81.78; H, 7.62; N, 10.60. Found: C, 81.76; H, 7.70; N, 10.68.

A solution of the crude imine base (8.0 g, 0.030 mole) in ethyl ether was treated with gaseous hydrogen chloride until no more solid precipitated. The resultant solid was recrystallized from methanol/ethyl acetate to obtain 8.9 g (98%) of *(R)*(−)-**6** sufficiently pure for the next reaction. Further recrystallization of a 1.43 g sample from methanol/ethyl acetate yielded 1.34 g of white crystals, mp 228-229°; $[\alpha]_D^{25}$ −4.4° (c 1.01, 100% ethanol).

Anal. Calcd. for $C_{18}H_{21}ClN_2$: C, 71.87; H, 7.04; N, 9.31. Found: C, 71.89; H, 7.08; N, 9.23.

(S)(+)-2-Imino-1,5-dimethyl-3,3-diphenylpyrrolidine Hydrochloride [*(S)*(+)-**6**].

The *(S)*(+)-imine base was prepared as described above from *(S)*(−)-**5** (12.0 g) in 64% crude yield. Recrystallization of a 3.2 g sample yielded 2.0 g of white needles; mp 118.5-119°; $[\alpha]_D^{25}$ +145° (c 1.01, 100% ethanol).

Anal. Calcd. for $C_{18}H_{20}N_2$: C, 81.78; H, 7.62; N, 10.60. Found: C, 81.82; H, 7.49; N, 10.62.

The hydrochloride salt was prepared as above from the crude imine base in 92% yield. A 1.60 g sample was recrystallized from methanol/ethyl acetate to obtain 1.37 g of white crystals, mp 228-229°; $[\alpha]_D^{25}$ +4.3° (c 1.01, 100% ethanol).

Anal. Calcd. for $C_{18}H_{21}ClN_2$: C, 71.87; H, 7.04; N, 9.31. Found: C, 71.97; H, 6.96; N, 9.31.

(R)(−)-1,5-Dimethyl-3,3-diphenyl-2-pyrrolidone [*(R)*(−)-**7**].

A mixture of *(R)*(−)-**6** (7.4 g, 0.025 mole) in 1.2*N* hydrochloric acid (100 ml) was added sodium nitrite (200 g). The mixture was heated 1 hour on a steam bath, then cooled. The precipitated solid was collected, washed with water, dried, and recrystallized from 100% ethanol to obtain 3.4 g of the pyrrolidone as a white solid, mp 148-149°; $[\alpha]_D^{25}$ −11.0° (c 1.01, 100% ethanol).

Anal. Calcd. for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.64; H, 7.25; N, 5.22.

The aqueous filtrate was basified with concentrated ammonium hydroxide and extracted with ethyl ether (3 ×). Evaporation of the dried (potassium carbonate) extracts gave 2.7 g of imine base. Therefore, the corrected yield of *(R)*(−)-**7** was 87%.

(S)(+)-1,5-Dimethyl-3,3-diphenyl-2-pyrrolidone [*(S)*(+)-**7**].

The *(S)*(+)-pyrrolidone was prepared as above from crude *(S)*(+)-**6** (5.0 g, 0.017 mole). The reaction yielded 3.35 g (76%) of white solid, mp 148-149°; $[\alpha]_D^{25}$ +11.0° (c 1.01, 100% ethanol).

Anal. Calcd. for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.47; H, 7.14; N, 5.24.

(R)(+)-2-Ethyl-1,5-dimethyl-3,3-diphenylpyrrolinium Perchlorate [*(R)*(+)-**8**].

With sonication *(R)*(−)-**7** (1.00 g, 0.0038 mole) was dissolved in dry toluene (20 ml). The resultant solution was added dropwise under a nitrogen atmosphere to a solution of ethyl lithium (3.0 ml, 1.25*M*) in benzene:ethyl ether (7:3). Afterwards, the reaction mixture was stirred at room temperature with additional ethyl lithium being added periodically until the starting material was consumed. The reaction was quenched with water and the volume brought to 200 ml with ethyl ether. The water was removed by pipette, and 60% perchloric acid was added until precipitation ceased. After overnight cooling, the salt was collected and recrystallized from methanol/ethyl acetate to obtain 0.73 g (51%) of product as white needles, mp 161-163.5°; $[\alpha]_D^{25}$ +61.6° (c 0.9, 100% ethanol); uv (methanol): λ max (ε) 237 (4200), 266 nm (2100).

Anal. Calcd. for $C_{20}H_{24}ClNO_4$: C, 63.57; H, 6.40; N, 3.71. Found: C, 63.43; H, 6.29; N, 3.62.

(S)(−)-2-Ethyl-1,5-dimethyl-3,3-diphenylpyrrolinium Perchlorate [*(S)*(−)-**8**].

This isomer was prepared in the same manner and on the same scale as the *(R)*-isomer. Recrystallization of the crude salt gave 0.87 g (60%) of product as white needles, mp 162-163°; $[\alpha]_D^{25}$ −62.0° (c 0.9, 100% ethanol); uv (methanol): λ max (ε) 237 (4400), 266 nm (2200).

Anal. Calcd. for $C_{20}H_{24}ClNO_4$: C, 63.57; H, 6.40; N, 3.71. Found: C, 63.00; H, 6.20; N, 3.64.

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[20] The ^{1}H-nmr data reported by Beckett and co-workers [11] on the optically active oxalate salts also indicated that no exchange took place in deuterium oxide solution.