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Asymmetric Homologation of Ketones. A New Entry to Orthogonally Protected (2*R*,4*R*)-Piperidine-2,4-dicarboxylic Acid

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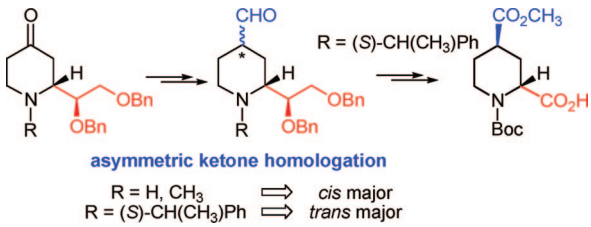

A new conformationally constrained analogue of glutamic acid has been synthesized efficiently in seven steps from a chiral 2-alkyl-4-piperidone. The synthesis is based on (a) the unprecedented asymmetric one-carbon homologation of the ketone controlled by the size of the N-substituent and (b) the appropriate manipulation of substituents at positions 2 and 4 of the piperidine ring, a step that involves two independent oxidation processes.

Conformationally constrained amino acids are useful structural components for pseudopeptides and peptidomimetics in drug discovery, as the introduction of appropriate conformational constraints provides a powerful strategy for improved drug design.[1] Replacement of a natural amino acid with a conformationally constrained analogue in biologically active peptides has often led to new compounds with improved properties and has provided new insights in the elucidation of receptor-bound ligand conformations.[2]

Glutamic acid is the principal excitatory neurotransmitter in the mammalian central nervous system and is involved in a variety of essential physiological functions, including neuronal plasticity and development, memory, and learning. This amino acid is also implicated in the pathogenesis of several acute, chronic, and neurodegenerative disorders such as cerebral ischemia, hypoxia, epilepsy, amyotrophic lateral sclerosis, and Parkinson's and Alzheimer's diseases.[3] In this context, the design and synthesis of conformationally constrained glutamic acid analogues is currently an active area of research[4] directed toward the development of potentially novel therapeutics to prevent or treat these diseases.[5]

Piperidine-2,4-dicarboxylic acid is a conformationally constrained glutamic acid analogue. This amino acid and its close derivatives have shown high affinity for TFN-α-converting enzyme (TACE), matrix metalloprotease (MMP), tachykinin, and *N*-methyl-D-aspartic acid (NMDA) subtype amino acid receptors.[6] The inhibition of these targets is important in the treatment of artherosclerotic lesions, inflammatory diseases, pain, asthma, and Alzheimer's disease.

It is known that each stereoisomer of a biologically active compound usually displays a different effect on a specific receptor. Piperidine-2,4-dicarboxylic acid has four stereoisomers: a pair of *cis*-enantiomers and a pair of *trans*-enantiomers. Racemic *trans*-piperidine-2,4-dicarboxylic acid is reported[6a] to

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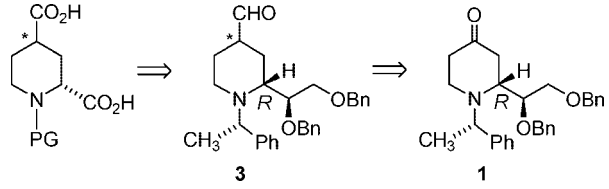
SCHEME 1. Retrosynthetic Analysis



behave as an agonist at the NMDA receptor. On the other hand, *cis*-piperidine-2,4-dicarboxylic acid has NMDA antagonist profiles. As a consequence, the efficient independent synthesis of any of the possible stereoisomers of piperidine-2,4-dicarboxylic acid represents a significant achievement due to the important physiological properties associated with its three-dimensional structure.

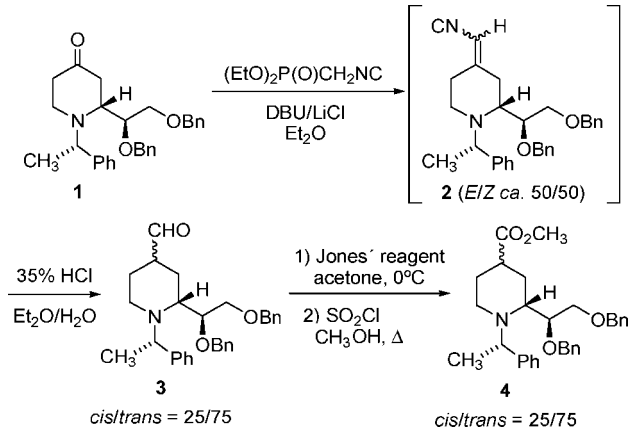
In spite of its biological relevance, only a few methods have been reported for the preparation of racemic *trans*- or *cis*-piperidine-2,4-dicarboxylic acid.[7] In addition, two asymmetric syntheses of enantiopure piperidine-2,4-dicarboxylic acid derivatives of 2*S* configuration have been described.[8]

In the course of our work on the asymmetric synthesis of polysubstituted piperidines from enantiopure (*R*)-2-[(*S*)-1,2-dibenzyloxyethyl]-1-[(*S*)-1-phenylethyl]-4-piperidone (**1**),[9] we envisaged that this compound could be a useful starting material for the preparation of piperidine-2,4-dicarboxylic acid derivatives with the *R* absolute configuration at C_2 (Scheme 1). The proposed strategy involves the use of aldehyde **3**, obtained by asymmetric one-carbon homologation of 4-piperidone **1**, as the key intermediate. Appropriate transformation of the piperidine ring substituents at C_2 and C_4 of aldehyde **3** would lead to the desired glutamic acid analogue.

In this paper, we report full details of the asymmetric synthesis of enantiomerically pure (2*R*,4*R*)-1-*tert*-butoxycarbonyl-4-methoxycarbonylpiperidine-2-carboxylic acid (**7**) from piperidone **1**. Compound **1** is easily available on gram scale from inexpensive D-mannitol.[10]

The addition of one carbon unit to a ketone to homologate it to a new carbonyl derivative is an important transformation that chemists have approached in different ways.[11] It is known that ketones and aldehydes react through a Wadsworth−Emmons olefination using diethyl isocyanomethylphosphonate to give α,β-unsaturated isocyanides.[12] Acidic hydrolysis of these latter compounds affords the corresponding homologated aldehydes.[13] This strategy has proven to be appropriate to homologate sterically hindered ketones, cyclic ketones, enolizable ketones,

SCHEME 2. Synthesis of Methyl Ester 4



and several aliphatic and aromatic aldehydes. Nevertheless, to the best of our knowledge, an asymmetric version of this synthetic methodology has yet to be reported.

Wadsworth−Emmons reaction of piperidone **1** with an excess of diethyl isocyanomethylphosphonate (5.0 equiv) under the reaction conditions described by Masamune and Roush[14] afforded intermediate α,β-unsaturated isocyanide **2** as a ca. 50/50 mixture of *Z*/*E* diastereoisomers,[15] which was hydrolyzed with HCl at room temperature in a two-phase system (diethyl ether/water) to afford aldehyde **3** as a thermodynamically unstable 25/75 mixture of *cis* and *trans* diastereoisomers.[15] On standing, the aldehyde of *trans* configuration slowly epimerized to the *cis* isomer to reach a constant value of 76/24 in favor of the *cis*-diastereoisomer after several days. Consequently, crude aldehyde **3** was dissolved in acetone and immediately oxidized with Jones' reagent and subsequently esterified by treatment with thionyl chloride/methanol to cleanly afford the corresponding methyl ester **4** as a 25/75 mixture of *cis*/*trans* diastereoisomers.[15] Configurationally stable methyl esters *cis*-**4** and *trans*-**4** were easily isolated by column chromatography in 14% and 44% yield, respectively, from starting 4-piperidone **1** (Scheme 2).

Conversion of *trans*-**4** into the conveniently protected (2*R*,4*R*)-piperidine-2,4-dicarboxylic acid derivative was performed as follows (Scheme 3). Selective hydrogenolytic N-debenzylation of *trans*-**4** using Pd on carbon as the catalyst and in the presence of Boc_2O gave *N*-Boc derivative **5** in 74% yield. Subsequent removal of the *O*-benzyl groups by extensive hydrogenolysis using $Pd(OH)_2$ on carbon as the catalyst afforded diol **6** in nearly quantitative yield. This compound was immediately submitted to oxidative cleavage by treatment with excess of sodium periodate in the presence of a catalytic amount of anhydrous ruthenium trichloride to give orthogonally protected (2*R*,4*R*)-piperidine-2,4-dicarboxylic acid **7** in 59% yield. A parallel synthetic scheme starting from *cis*-**3** could not be completed as diol of *cis* configuration suffered an immediate lactonization process.

Preferential formation of aldehyde **3** of *trans* configuration in the homologation process indicated that hydrolysis of isocyanide **2** had mainly occurred from the side of the piperidine ring where the bulky 1,2-dibenzyloxyethyl substituent at C_2 is

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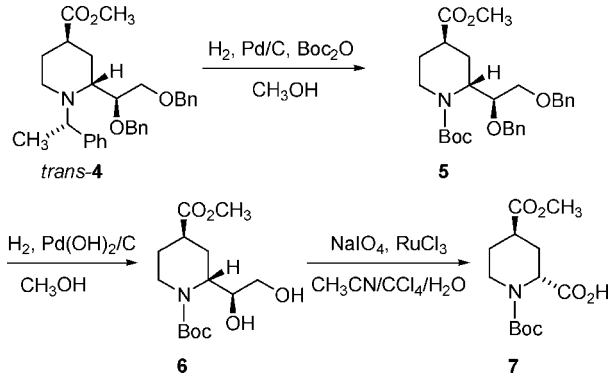
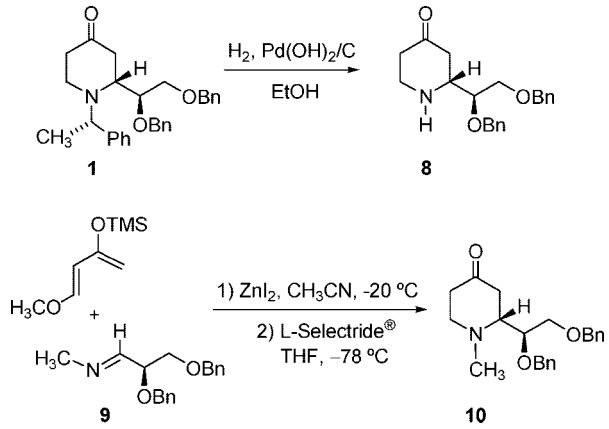
(15) Diastereomeric ratios were determined by ^1H NMR analysis of crude reaction mixtures. The *E* and *Z* or *cis* and *trans* configurations were unambiguously assigned by 2D $^1H-^1H$ NOESY experiments.

SCHEME 3. Synthesis of Orthogonally Protected (2*R*,4*R*)-Piperidine-2,4-dicarboxylic Acid from Ester *trans*-4



SCHEME 4. Synthesis of Piperidones 8 and 10



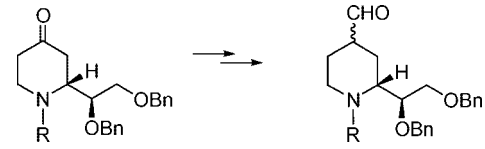
located. In an effort to rationalize this stereochemical course, some additional investigations were carried out.

Piperidones **8** and **10**, in which the bulky *N*-[(*S*)-1-phenylethyl] substituent has been replaced with much less sterically demanding groups (hydrogen and methyl), were prepared as follows. Compound **8** was obtained by N-debenzylation of **1** with molecular hydrogen in the presence of $Pd(OH)_2/C$ as the catalyst (Scheme 4). Compound **10** was prepared through a synthetic route similar to that previously described for piperidone **1**. Treatment of (*R*)-2,3-di-*O*-benzyl-glyceraldehyde with methylamine in the presence of anhydrous $MgSO_4$ afforded crude imine **9**. This compound reacted with Danishefsky's diene in the presence of ZnI_2 as a catalyst at low temperature and using anhydrous acetonitrile as solvent to give a cyclic enaminone (dr = 93/7), which upon regioselective reduction with L-Selectride at −78 °C, followed by purification by column chromatography, afforded enantiomerically pure piperidone **10** (Scheme 4).

The homologation process was investigated next. Treatment of piperidones **8** and **10** with an excess of diethyl isocyanomethylphosphonate using DBU as a base, in the presence of LiCl, and subsequent acidic hydrolysis gave aldehydes **11** and **12**, which were obtained, respectively, as 86/14 and 72/28 *cis*/*trans* thermodynamically stable diastereomeric mixtures[15] in which the *cis*-diastereoisomer predominated (Table 1).

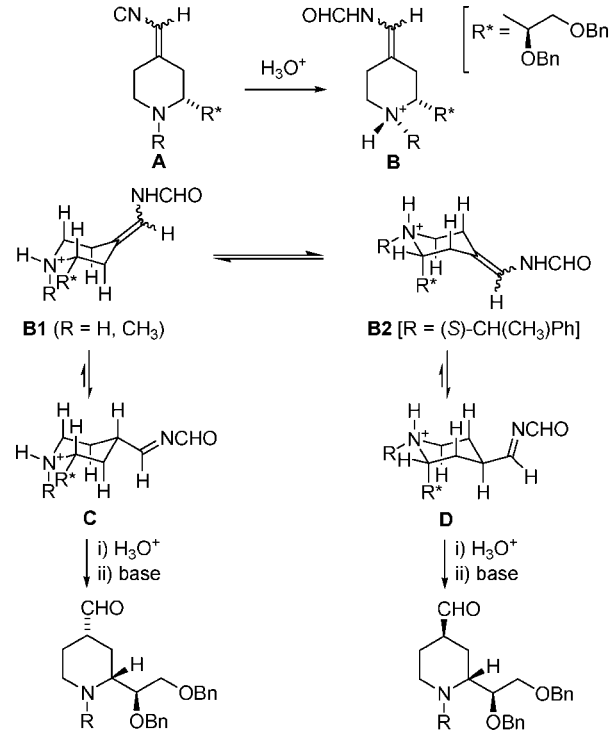
These results indicate that the stereochemical course of the homologation reaction of piperidones **1**, **8**, and **10** via an α,β-unsaturated isocyanide depends on the size of the R substituent on the nitrogen. When R is the bulky (*S*)-1-phenylethyl group, *trans*-**3** is obtained as the major product, whereas when R is a small group, such as hydrogen or methyl, *cis*-**11** and *cis*-**12**, respectively, are obtained in excess.

TABLE 1. Homologation Process for Piperidones 1, 8, and 10



entry	R	substrate	product	*cis*/*trans*
1	(*S*)-CH(CH$_3$)Ph	**1**	**3**	25/75
2	H	**8**	**11**	86/14
3	CH$_3$	**10**	**12**	72/28

SCHEME 5. Stereochemical Course of the Isocyanide Hydrolysis



An attempt to rationalize the stereochemical course of the formation of aldehydes **3**, **11**, and **12** by acidic hydrolysis of the isocyanides **1**, **8**, and **10** is made below.

Acidic treatment of isocyanides **A** led to hydration of the isonitrile group with concomitant protonation of the nitrogen of the ring opposite to the C_2 substituent to afford the corresponding *N*-formylenamine **B**. Depending on the R substituent on the nitrogen, the conformational equilibrium would be shifted to conformer **B1** (small-sized substituents) or conformer **B2** [bulky (*S*)-1-phenylethyl group].

The initially formed *N*-formylenamine evolves to the corresponding *N*-formylimine in which bulky substituents are situated in an equatorial disposition through an enamine-imine tautomeric equilibrium. Subsequent hydrolysis of the formylimino group in 1,2,4-trisubstituted piperidinium salts **C** or **D** followed by neutralization led to the preferential formation of the corresponding aldehyde of *cis* or *trans* configuration (Scheme 5).

In conclusion, (2*R*,4*R*)-*N*-*tert*-butoxycarbonyl-4-methoxycarbonylpiperidine-2-carboxylic acid **7** has been obtained from 4-piperidone **1** in 19% overall yield. The route is a simple procedure that is based on a novel diastereoselective one-carbon

homologation process of ketones via α,β-unsaturated isocyanides. The procedure described here constitutes (a) the first asymmetric synthesis of a piperidine-2,4-dicarboxylic acid derivative with 2*R* configuration and (b) the first example of an asymmetric homologation of ketones of this type. This synthesis, which avoids low reaction temperatures and difficult purification procedures, highlights the utility of 4-piperidone **1** as a versatile chiral precursor for the stereoselective synthesis of biologically active polysubstituted piperidines.

Experimental Section

Asymmetric Homologation of Piperidone 1. To a suspension of anhydrous lithium chloride (424 mg, 10.0 mmol) in anhydrous Et_2O (10 mL) at room temperature under argon were added diethyl isocyanomethylphosphonate (1.60 mL, 10.0 mmol) and DBU (1.64 mL, 11.0 mmol). The mixture was stirred for 10 min at room temperature. A solution of compound **1** (886 mg, 2.0 mmol) in anhydrous Et_2O (30 mL) was added, and the resulting mixture was stirred at room temperature for 24 h. The reaction was quenched with 35 wt % hydrochloric acid in water (33 mL), and the biphasic Et_2O/H_2O mixture was stirred at room temperature for 7 h. The reaction mixture was cooled to 0 °C, neutralized with solid K_2CO_3, and extracted with Et_2O (3 × 50 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure to yield compound **3** as a 25/75 *cis*/*trans* mixture of diastereoisomers. A solution of the obtained compound in $CHCl_3$ (50 mL) was stirred under reflux conditions for 7 d and evaporated under reduced pressure to yield compound **3** as a 76/24 *cis*/*trans* mixture of diastereoisomers.

(2*R*,4*R*)-2-[(*S*)-1,2-Dibenzyloxyethyl]-1-[(*S*)-1-phenylethyl]piperidine-4-carbaldehyde (*trans*-3). From the 25/75 *cis*/*trans* mixture obtained in the acidic hydrolysis of (*E*/*Z*)-**2**: IR absorptions (neat) ν_{max} 1724; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (3H, d, J = 6.6), 1.44 (1H, ddd, J = 12.6, J = 8.6, J = 4.4), 1.47−1.54 (1H, m), 1.58−1.67 (1H, m), 2.11 (1H, ddd, J = 11.8, J = 7.7, J = 4.4), 2.35 (1H, ddd, J = 12.4, J = 7.6, J = 3.4), 2.45−2.52 (1H, m), 2.49−2.56 (1H, m), 2.89−2.95 (1H, m), 3.59 (1H, dd, J = 10.6, J = 6.4), 3.73 (1H, dd, J = 10.6, J = 2.5), 3.89−3.94 (1H, m), 3.95 (1H, q, J = 6.6), 4.42 (1H, d, J = 12.0), 4.49 (1H, d, J = 12.0), 4.59 (1H, d, J = 11.7), 4.72 (1H, d, J = 11.7), 7.06−7.35 (15H, m), 9.51 (1H, bs); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.9, 23.4, 24.6, 42.2, 45.1, 55.0, 57.1, 71.4, 72.7, 73.4, 78.5, 126.5, 127.3, 127.5, 127.6, 127.7, 127.8, 128.0, 128.2, 128.3, 138.2, 138.8, 145.3, 204.7; HRMS (ESI+) calcd for $C_{30}H_{36}NO_3$ (MH^+) 458.2690, found 458.2695.

(2*R*,4*S*)-2-[(*S*)-1,2-Dibenzyloxyethyl]-1-[(*S*)-1-phenylethyl]piperidine-4-carbaldehyde (*cis*-3). From the 76/24 *cis*/*trans* mixture obtained in the epimerization of (*cis*/*trans*)-**3**: IR absorptions (neat) ν_{max} 1724; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11−1.22 (2H, m), 1.12 (3H, d, J = 6.9), 1.59 (1H, bd, J = 12.6), 1.99 (1H, ddd, J = 11.6, J = 11.6, J = 2.4), 2.03−2.13 (1H, m), 2.26 (1H, ddd, J = 12.6, J = 3.3, J = 2.3), 2.43 (1H, ddd, J = 11.6, J = 3.5, J = 3.5), 2.69 (1H, ddd, J = 11.2, J = 4.1, J = 2.3), 3.63 (1H, dd, J = 10.6, J = 7.6), 3.98 (1H, dd, J = 10.6, J = 0.9), 4.06−4.12 (1H, m), 4.08 (1H, q, J = 6.9), 4.43 (1H, d, J = 12.1), 4.54 (1H, d, J = 12.1), 4.65 (1H, d, J = 12.0), 4.79 (1H, d, J = 12.0), 7.11−7.36 (15H, m), 9.51 (1H, d, J = 1.3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.0, 25.7, 26.1, 44.2, 49.2, 53.8, 59.0, 71.1, 72.8, 73.6, 77.6, 126.5, 127.5, 127.5, 127.6, 127.6, 127.7, 128.0, 128.3, 128.4, 138.2, 138.8, 143.4, 203.7; HRMS (ESI+) calcd for $C_{30}H_{36}NO_3$ (MH^+) 458.2690, found 458.2677.

(2*R*,4*R*)-1-*tert*-Butoxycarbonyl-4-methoxycarbonylpiperidine-2-carboxylic Acid (7).[16] $NaIO_4$ (428 mg, 2.0 mmol) was added to a stirred solution of compound **6** (152 mg, 0.5 mmol) in $CH_3CN/CCl_4/H_2O$ (2:2:3, 14 mL). After being vigorously stirred for 5 min, the mixture was treated with anhydrous $RuCl_3$ (5 mg, 0.025 mmol), and stirring was continued for 3 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and water (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic layers were dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo. Purification of the crude product by column chromatography (eluent: EtOAc/hexanes 2:1) afforded 85 mg (59%) of compound **7** as a white solid: white solid; mp = 102−104 °C; $[\alpha]^{25}_D$ = +17.2 (*c* 0.47, $CHCl_3$); IR absorption (KBr) 3700−2250, 1734, 1717, 1699, 1257 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.44 and 1.47 (s, 9H), 1.56 (dddd, 1H, J = 13.0, J = 13.0, J = 12.5, J = 4.6), 1.76−1.89 (m, 1H), 1.93 and 1.99 (bd, 1H, J = 13.0 and J = 13.0), 2.41 (bdd, 1H, J = 13.0, J = 13.0), 2.46 and 2.51 (bd, 1H, J = 13.1 and J = 13.6), 2.92 and 3.02 (bdd, 1H, J = 12.6, J = 12.6 and J = 12.4, J = 12.4), 3.69 (s, 3H), 4.02 and 4.13 (bd, 1H, J = 12.4 and J = 12.6), 4.87 and 5.04 (bd, 1H, J = 4.6 and J = 4.7), 8.33 (bs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.4 and 27.5, 28.2 and 28.3, 28.6, 37.9 and 38.0, 40.2 and 41.1, 51.9, 52.8 and 53.8, 80.7 and 80.8, 155.1 and 155.8, 174.6, 176.4 and 176.7; HRMS (ESI^-) calcd for $C_{13}H_{20}NO_6$ ($M-H^+$) 286.1296, found 286.1293. Anal. Calcd for $C_{13}H_{21}NO_6$: C, 54.35; H, 7.37; N, 4.88. Found: C, 54.27; H, 7.68; N, 4.52.

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Supporting Information Available: General statement describing materials and methods, additional experimental procedures, physical and spectral data (^{1}H NMR, ^{13}C NMR, and IR) for all new compounds, and NOESY spectrum for compound **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) NMR data of compound **7** correspond to two conformers detected at room temperature whose well-resolved signals at room temperature did not collapse to a well-resolved spectrum even at 353 K in C_6D_6. In the NOESY spectrum, duplicate signals clearly show exchange cross peaks.