Synthesis of an Actinomycin-Related Peptide, *cyclo*-(Thr-D-Val-Pro-Sar-MeAla), and Conformational Studies by Nuclear Magnetic Resonance and X-ray Crystallography

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Abstract: The cyclic pentapeptide *cyclo*-(Thr-D-Val-Pro-Sar-MeAla) (I) was synthesized via its crystalline (Thr)-*O*-benzyl derivative (II). The amino acid sequence of I is related to that of the peptide lactone moiety of actinomycins. An X-ray crystallographic structure of II was obtained, which featured trans peptide bonds, a Sar-MeAla β turn, and a possible (long) 4→1 (Thr→Pro) hydrogen bond. Proton and ^{13}C NMR parameters are compatible with a similar ring conformation for I and II in solution. Comparisons are made with conformational studies reported for other cyclic pentapeptides.

Introduction

Conformational investigations of cyclic pentapeptides began about a decade ago and have recently accelerated.[1-16] Solution conformations have not always corresponded with crystal structures. In compounds containing sarcosine, the presence of cis peptide bonds was observed.[3-6] In other cases, the predominant conformations were all trans, and attention focused upon questions of internal hydrogen bonding and the presence of β and γ turns. Solution studies of a pentapeptide lactone representing half of the actinomycin D molecule have also been described,[17-19] which featured solvent-dependent conformational duality. The present study involves the title compound (I) and its crystalline (Thr)-*O*-benzyl derivative (II). The peptide lactone structure present in the actinomycins is related to I via an N,O-acyl shift; the possibility of exploring this transformation experimentally prompted the synthesis of I. Its amino acid sequence corresponds to that of actinomycin D, except for the replacement of *N*-methylvaline by *N*-methylalanine; this replacement occurs naturally in the actinomycin Z complex.[20] The sequence also bears some resemblance to that of *cyclo*-(Gly-Pro-Ser-D-Ala-Pro), which has been the subject of X-ray crystallographic[12] and solution[13] studies. The latter molecule adopts quite different conformations in the crystal and in solution. The present study includes NMR (^1H and ^{13}C) and X-ray crystallographic studies, some of which have been reported briefly in preliminary form.[21]

Results and Discussion

Synthesis. The pentapeptide H-MeAla-Thr(OBz)-D-Val-Pro-Sar-OH, which was synthesized by conventional solution techniques (Figure 1), was cyclized with dicyclohexylcarbodiimide to afford the crystalline cyclic pentapeptide II. Catalytic hydrogenation of II produced the noncrystalline cyclopeptide I.

^1H NMR. The proton chemical shifts of I and II in several solvents are given in Table I, and the various coupling constants are listed in the Experimental Section. A 600-MHz spectrum of II in $CDCl_3$ is shown in Figure 2. There is no evidence for conformational heterogeneity on the NMR time scale, and no apparent conformational change upon removal of the benzyl group (II → I). The benzene shifts of the two *N*-methyl groups are large and equal, an observation compatible with the presence of trans Pro-Sar and Sar-MeAla peptide bonds. The behavior of the two NH protons of II suggests that the valyl NH is exposed to solvent, whereas the threonyl NH is not and is probably internally hydrogen bonded. Thus, (i) the valyl NH undergoes a large (~1 ppm) downfield shift upon changing the solvent from chloroform to dimethyl sulfoxide, whereas the threonyl NH shifts slightly upfield; (ii) the temperature dependence of the NH shifts in methanol is much greater for that of valine ($\Delta\delta/\Delta T = 9.10 \times 10^{-3}$ ppm deg^{-1}) than for that of threonine ($\Delta\delta/\Delta T = 2.28 \times 10^{-3}$); and (iii) the rate of deuterium exchange of the valine NH (upon addition of methanol-d_4 to a solution of II in $CDCl_3$) was approximately 50 times as great as that of threonine.

The $^3J_{NH,C_\alpha H}$ values for threonine and valine in II both correspond with dihedral angles close to 180°, based upon the equation[22]

$$J = 7.9 \cos^2\theta - 1.55 \cos\theta + 1.35 \sin^2\theta$$

The $J_{\alpha\beta}$ values correspond with dihedral angles of 90 and 156° for threonine and valine, respectively, based upon the equation[23]

$$J = 11.0 \cos^2\theta - 1.4 \cos\theta + 1.6 \sin^2\theta$$

When the latter relationship is applied to the $J_{\alpha\beta}$ values for proline, dihedral angles of 13 and 118° are obtained. Comparison of these values with those observed in the crystal structure must allow for the approximate nature of such empirical relations and the possibility of rapid equilibria among different conformations of the proline ring.

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Table I. Proton NMR Chemical Shifts (δ) of Cyclopeptides I and II

	II				I		
	$CDCl_3$	$CDCl_3/C_6D_6$[a]	CD_3COCD_3	CD_3SOCD_3	$CDCl_3$	CD_2Cl_2	CD_3SOCD_3
NH Thr	7.48	7.40	7.53	obsc	7.46	7.45	7.24
NH Val	6.20	6.20	6.23	6.85	6.25	6.22	7.19
MeAla α	5.47	5.48	5.27	5.11	5.51	5.42	5.02
Pro α	4.95	4.69	4.99	4.91	4.91	4.88	4.89
Thr α	4.74	4.79	obsc	obsc	4.69	4.63	obsc
Bz CH_2	4.60	4.55	4.60	4.51			
Thr β	4.58	obsc	obsc	obsc	4.44	4.31	4.22
Sar α	4.56	4.15	4.61	4.43	4.63	4.57	obsc
	3.15	2.63	3.30	3.28	3.18	3.16	obsc
Val α	4.39	4.43	4.37	4.25	4.42	4.41	obsc
N-CH_3	3.40	3.07	3.38	3.25	3.41	3.35	3.23
	3.09	2.74	3.13	2.97	3.08	3.03	2.99
MeAla CCH_3	1.44	1.33	1.38	1.30	1.44	1.40	1.29
Thr CH_3	1.13	1.09	1.12	1.09	1.12	1.07	1.00
Val CH_3	0.93	0.97	0.91	0.86	0.95	0.93	0.85
	0.88	0.89	0.87	0.82	0.89	0.89	0.81

[a] 1:1 (v/v).

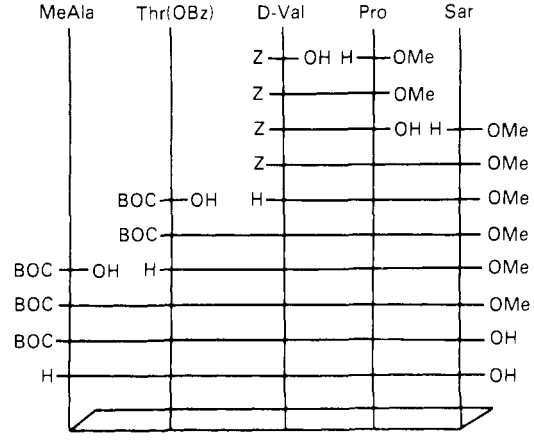

Figure 1. Scheme for synthesis of the cyclopentapeptide II.

^{13}C NMR. The ^{13}C chemical shift assignments of II in $CDCl_3$ are shown in Figure 3. The spectra confirm the absence of conformational heterogeneity on the NMR time scale in this solvent. The chemical shift of the proline β carbon is compatible[24] with the presence of a trans Val-Pro peptide bond, in contrast to the case of actinomycin D[18,25] (28 compared with 31 ppm, respectively). Striking differences are also apparent in α-carbon chemical shifts, which in the case of II are closer to those reported for the isolated pentapeptide lactone[18,19] (in chloroform) than to those of actinomycin.

Solution Conformation of I and II. The combined evidence of ^1H and ^{13}C NMR suggests that those peptide bonds which might tend to adopt the cis conformation (Val-Pro, Pro-Sar, and Sar-MeAla) are trans. Accordingly, an all-trans space-filling (CPK) molecular model was constructed which also satisifed the requirement of a sequestered threonyl NH and exposed valyl NH. The resulting model has a 4→1 (Thr→Pro) hydrogen bond and a Sar-MeAla β turn. This conformation is similar to that revealed by X-ray crystallography (see below). The values of the parameters which approximate those expected for this geometry include (i) $^3J_{NH,C\alpha H}$ coupling constants[21], (ii) the ^2J of the sarcosine α protons[26] (14.5 Hz), and (iii) the chemical shift difference between the C^β and C^γ of proline (3.5 ppm) which corresponds[27] to ψ = 137°.

The crystal structure[12] of the related *cyclo*-(Gly-Pro-Ser-D-Ala-Pro) shows some similarity to II, but the solution conformation[13] is very different. The latter involves a hydrogen-bonded NH of glycine. The cyclic peptide II cannot adopt this conformation since sarcosine occupies the analogous site. NMR studies[17-19] of a synthetic pentapeptide lactone, representing half of the actinomycin D molecule, show a conformation in chloroform with a hydrogen-bonded valyl NH. In acetone solution, a different conformation is adopted with two cis peptide bonds (as in actinomycin). No parallel phenomena are seen in the case of II, spectra of which are essentially the same in both solvents.

X-ray Crystallography of II

Bond lengths and angles are given in Table II. The molecular conformations of the two independent molecules are shown in Figure 4 (ORTEP[28] drawing) and the conformational angles for the peptide rings are shown in Figure 5 (PLUTO[29] drawing). The proline ring of the second molecule is in a fairly typical half-chair conformation. Because of the disorder discussed in the Experimental Section, one cannot be certain of the comparable conformation in the first molecule but it is possible to fit two different half-chair conformations for the proline ring of the first molecule within the 50% apparent thermal ellipsoids.

In the remainder of this discussion, dimensions involving the disordered C^γ are implicitly omitted. The most obvious conformational difference between the two independent molecules lies in the different positions of the two benzyl groups. The conformational angles (Figure 5) of the two molecules are quite similar and appear to indicate that the conformation adopted for the peptide ring in the crystal may be similar to that in solution since the different packing forces exerted on the molecules do not produce radical changes. It will be noted that all peptide linkages are trans although the Val-Pro linkage shows considerable deviation from planarity, having an average angle of 156°. Deviations from planarity of peptide linkages have been observed previously; angles as small as 160° have been observed in two similar pentapeptides.[10,12] The agreement among comparable bond lengths and angles in the two crystallographically independent molecules is satisfactory. It is interesting to note that both valine residues are non planar at C′. The average dimensions of the peptide groups (Table III) are fairly similar to the literature averages[30] although there is considerable individual variation among comparable values.

The specifically crystallographic evidence for hydrogen bonding in II is somewhat indefinite. There is a relatively close approach

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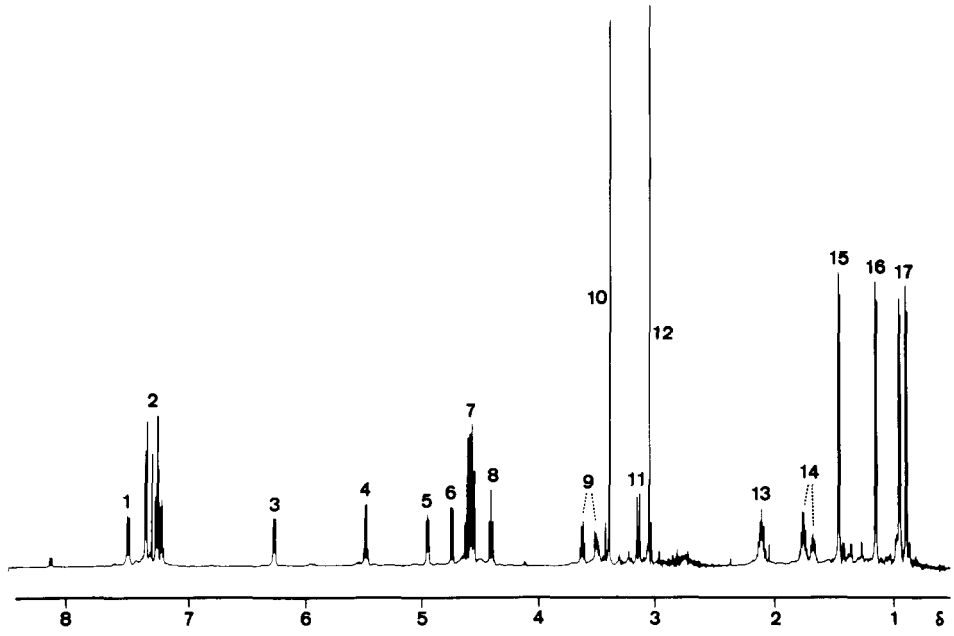

Figure 2. Proton NMR spectrum of II in $CDCl_3$ at 600 MHz: (1) Thr NH; (2) Ar-H; (3) Val NH; (4) MeAla α-H; (5) Pro α-H; (6) Thr α-H; (7) Sar α-H, Thr β-H, and Bzl CH_2; (8) Val α-H; (9) Pro δ-H; (10 and 12) N-CH_3; (11) Sar α-H; (13) Pro and Val β-H; (14) Pro β- and γ-H; (15) MeAla C-CH_3; (16) Thr CH_3; (17) Val CH_3 (2).

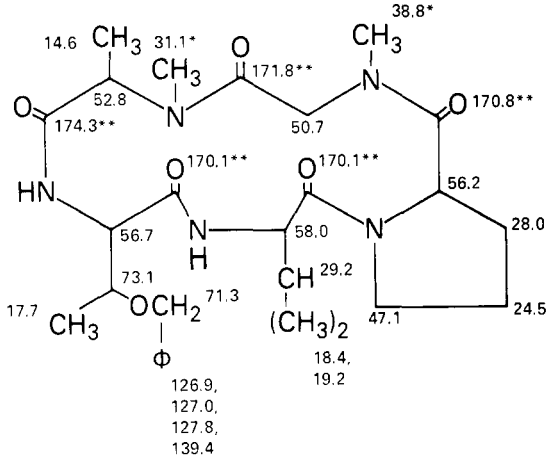

Figure 3. ^{13}C chemical shifts of II. Starred shifts may be interchanged.

of N(threonine) to O(proline), but the distances in the two molecules (3.22 and 3.30 Å, respectively) are of the order of van der Waals interactions. The appropriate H···O distances, in the two molecules, are 2.51 and 2.43 Å. The two distances are slightly less than the sum of the van der Waals radii[31] (2.72 Å) and it is possible that a very weak hydrogen bond does exist. The angles at the hydrogen atoms are compatible with the hypothesis, being 142 and 157°, respectively. There is spectroscopic evidence for such a hydrogen bond in solution, as mentioned elsewhere, and it seems likely that the rather weak bond is being stretched by packing forces in the crystal. It might be noted that long intramolecular hydrogen bonds have been observed previously in peptides; e.g., a bond of length 3.20 Å has been reported in *cyclo*-(L-Ala-L-Pro-D-Phe)$_2$.[32]

As the density indicates, the molecular packing is relatively efficient although no hydrogen bonds connect the molecules. The two independent molecules are oriented differently, are at different heights in the crystal, and are arranged around different twofold screw axes. The mean planes of the two independent peptide rings are approximately at right angles to each other. Despite the different orientations, the space between the molecules parallel to the *ac* plane is efficiently filled by each set of molecules. The two layers of molecules contact each other along the *b* axis, but a large gap is left on the other side of the contact plane which accommodates the roughly parallel phenyl rings of both sets of molecules.

However, because of the different molecular orientations, there are considerable differences in the associations of the benzene rings with the proline rings of the two molecules. The benzene ring of the second molecule is sandwiched between two proline rings, roughly parallel to its own proline ring and nearly at right angles to that in the other molecule. The benzene ring of the first molecule is nearly at right angles to its own proline ring but is not associated with that of the second molecule. The rings of the benzene layer are not particularly close to each other and the somewhat high thermal parameters are thus appropriate. The different orientations of the two independent proline rings with respect to the benzene rings probably explain the conformational disorder. The atoms of the first proline ring have very few short contacts with the benzene ring of the molecule and it seems likely that the proline ring conformation is not strongly controlled by atomic contacts. In contrast, the proline ring of the second molecule makes several contacts less than 3.6 Å, and, in this case, given the roughly parallel orientations of the two rings, it is obvious that conformational change would alter the situation greatly. The proline ring of the first molecule does approach the benzene ring of the second, but the mean planes of the rings are nearly at right angles and conformational change would not change the contact distances significantly.

The unusual Val-Pro ω angle of 156° in both independent molecules may also be a packing phenomenom since the deviation from 180° increases the distance of the proline rings from the benzene rings in the crystal. However, unless the near equality of the angles in the two independent molecules is fortuitous, forces exerted by interaction with the benzene rings do not seem the most likely cause of the nonplanarity; the orientations of the phenyl rings are quite different in the two independent molecules. Inspection of models discloses that, if the angle were 180°, O(valine) would be rather close to a C^δ proton of the proline ring. The observed change makes the C^δ-N-C′-O torsion angle close to 180° and increases the contact distance to over 3.6 Å. In general, the observed crystal conformation for II achieves good nonbonded contacts and the observed hydrogen atom positions are close to where one would place them, assuming gauche conformations.

In contrast with the cyclic hexapeptides, the number of crystal structures of cyclic pentapeptides reported in the literature is quite small. Karle has reported two structures,[10,12] those of *cyclo*-

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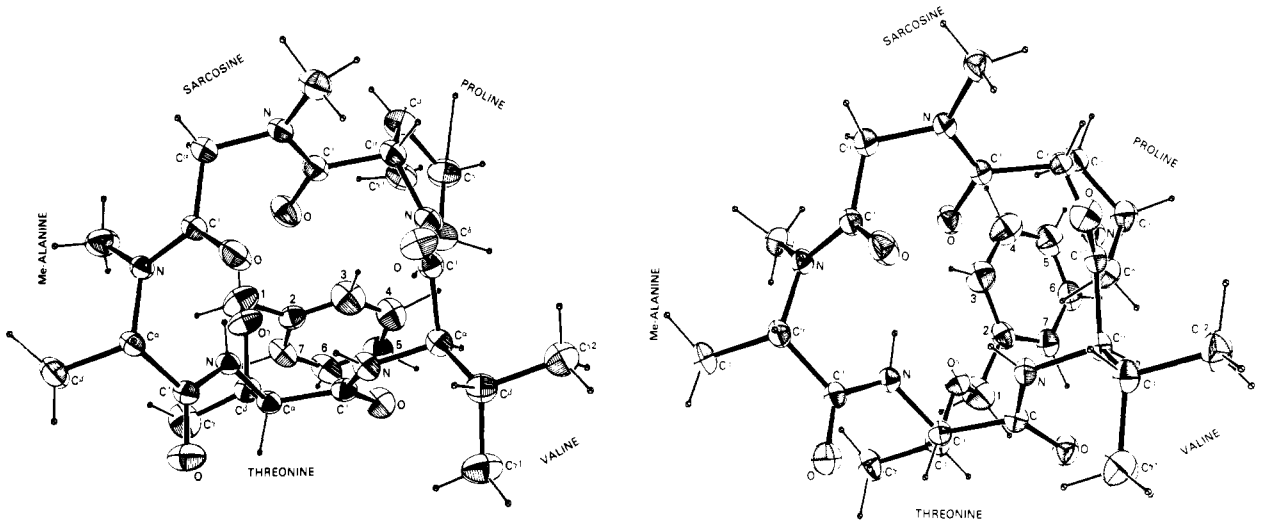

Figure 4. Crystal conformation and nomenclature of the two independent molecules. The thermal ellipsoids are drawn at a 25% probability level, in an attempt to show both the peptide and the benzyl side chain. The hydrogen atoms are represented by arbitrary spheres.

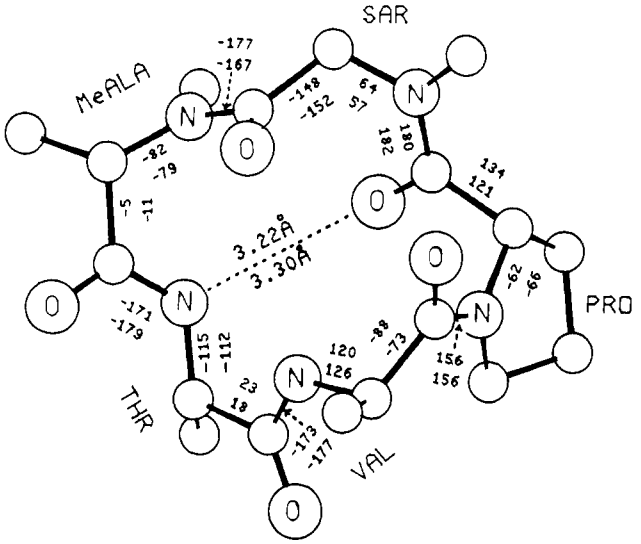

Figure 5. ω, ϕ, and ψ conformational angles for the two independent molecules. The possible hydrogen bond is also indicated. For each pair of values, that referring to the molecule designated the "first" in the text is always uppermost.

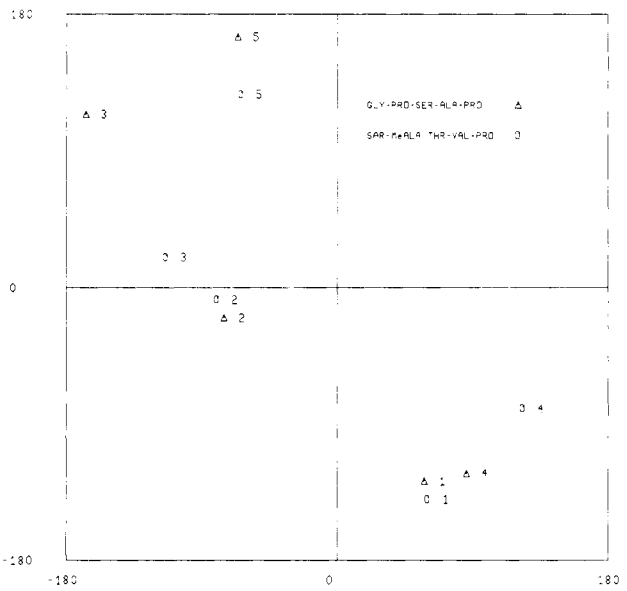

Figure 6. ψ–ϕ diagram for *cyclo*-(Gly-Pro-Ser-D-Ala-Pro) and the present structure (ϕ horizontal, ψ vertical). The sequence of residues for the latter has been changed from that in the text in order to make the residue numbers the same as *cyclo*-(Gly-Pro-Ser-D-Ala-Pro).

(Gly-Pro-Gly-D-Ala-Pro) and *cyclo*-(Gly-Pro-Ser-D-Ala-Pro), all the linkages of which are trans, and which allow direct comparison with the present study. *cyclo*-(Ala-Sar_4)[4] and *cyclo*-(Sar_5)[5] have cis–cis–cis–trans–trans linkages and are thus not directly comparable with the present structure. The structure of the toxic, chlorine-containing, cyclic pentapeptide, cyclochlorotine, has been described.[33] The molecule has an internal hydrogen bond but full crystal structural details were not given.

The two structures reported by Karle have very similar conformations[12] although the first possesses two internal hydrogen bonds and the second only one; it will suffice to compare the present structure with that with one hydrogen bond, *cyclo*-(Gly-Pro-Ser-D-Ala-Pro), hereafter GPSAP. GPSAP has a 4→1 hydrogen bond of type II′ in the notation of Venkatachalam[34] (torsion angles, after conversion to the current convention:[35] 60°, −120°, −80°, 0°). If one admits the existence of a hydrogen bond in the present structure, it is also a 4→1 bond of type II′. The appropriate ϕ–ψ–ϕ–ψ angles are 60°, −150°, −80°, −6° (average) for II and 60°, −128°, −75°, 20° in GPSAP.

The ϕ and ψ torsion angles for the peptide residues in the two structures are compared in Figure 6; the first two residues have very similar conformations but the third deviates greatly. The deviations decrease through the fourth and fifth residues. If one compares Figure 5 with Karle's corresponding diagram,[12] the similarities of the Pro^5-Gly^1-Pro^2-Ser^3 backbone in GPSAP to that of the Pro-Sar-MeAla-Thr portion of the present structure are also quite apparent. As indicated in Figure 6, the linkage Thr-D-Val, in the present structure, corresponds to Ser-D-Ala in GPSAP and the corresponding ϕ–ψ angles are (−114°, 20°) and (−167°, 114°), respectively.

Experimental Section

Column chromatography of fully protected peptide intermediates was effected as specified below. "Acid-washed alumina" refers to alumina (Brockmann activity I) which has been stirred with 10% acetic acid at 70 °C for 2 h, then washed with hot water until the washings are pH 5 and finally with methanol, and dried in air. Fractions from columns were monitored by thin-layer chromatography in various solvent systems, which was also a criterion of purity. Noncrystalline intermediates were characterized by chemical ionization mass spectroscopy (CIMS) and/or amino acid analysis (see below) as specified.

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Table II. Molecular Dimensions for the Peptide Components of the Molecules (Heavier Atoms)[a]

bonds (Å)	Pro(1)	Sar(2)	Me-Ala(3)	Thr(4)	Val(5)
$C^{\alpha}(i)$-C'(i)	1.538	1.517	1.520	1.539	1.514
	1.528	1.529	1.525	1.532	1.536
$C^{\alpha}(i)$-N(i)	1.469	1.463	1.474	1.452	1.471
	1.475	1.461	1.467	1.454	1.460
C'(i)-N(i+1)	1.331	1.350	1.334	1.343	1.351
	1.342	1.342	1.339	1.341	1.341
C'(i)-O(i)	1.241	1.218	1.227	1.215	1.229
	1.237	1.227	1.229	1.217	1.225
C^{α}-C^{β}	1.535		1.528	1.519	1.530
	1.540		1.528	1.521	1.527
C^{β}-C^{γ}	1.37, 1.61			1.513	1.518, 1.526
	1.527			1.505	1.525, 1.519
C^{γ}-C^{δ}	1.64, 1.49				
	1.523				
N-C^{δ}	1.463				
	1.461				
N-C(Me)		1.461	1.459		
		1.460	1.459		
C^{β}-O^{γ}				1.432	
				1.437	
N-C^{α}-C'	107.8	110.8	113.0	112.6	102.8
	105.8	111.5	113.9	113.2	104.5
C^{α}-C'-N(i+1)	119.9	120.0	118.2	115.4	118.3
	121.5	119.3	118.9	115.8	116.5
C^{α}-C'-O	119.3	119.3	119.1	120.9	120.8
	118.2	119.2	118.6	120.6	121.4
O-C'-N(i+1)	120.8	120.7	122.7	123.6	120.5
	120.2	121.5	122.5	123.5	121.6
C'-N(i+1)-Me(i+1)	124.7	123.8			
	126.1	124.3			
C'-N(i+1)-C^{α}(i+1)	114.8	116.5	123.7	123.9	118.5
	115.0	116.1	121.5	123.6	119.9
Me-N-C^{α}		118.4	119.4		
		118.1	119.4		
N-C^{α}-C^{β}	104.0		113.3	110.2	112.5
	103.8		113.4	112.5	112.9
C^{β}-C^{α}-C'	111.0		109.9	112.8	113.2
	111.1		109.3	112.0	112.7
C^{α}-C^{β}-C^{γ}				111.4	110.3, 110.1
	105.5			112.9	110.8, 111.0
C^{β}-C^{γ}-C^{δ}					
	102.6				
C^{γ}-C^{δ}-N					
	102.0				
C^{δ}-N-C^{α}	113.0				
	110.3				
C'-N(i+1)-C^{δ}(i+1)					127.1
					128.7
$C^{\gamma 1}$-C^{β}-$C^{\gamma 2}$					110.5
					109.9
C^{α}-C^{β}-O^{γ}				104.9	
				106.3	
C^{γ}-C^{β}-O^{γ}				112.1	
				112.6	

[a] Esd's are less than 0.004 Å in the peptide ring and less than 0.006 Å for peripheral substituents. The formal esd's are less than 0.01 Å for bonds involving the disordered C^{γ} of the first molecule. The pairs of values for valine C^{γ} refer to $C^{\gamma 1}$ and $C^{\gamma 2}$. Esd's of angles are less than 0.3° and angles involving the disordered C^{γ} of the first molecule are omitted.

Amino acid analyses were obtained by gas–liquid chromatography after derivatization of hydrolyzate constituents as trifluoroacetylated methyl esters. On column A (3% OV17 on Gas Chrom Q, 100–120 mesh) at 70 °C, with a 4°/min temperature program, retention times (min) were: Thr, 4.5; Val, 5.3; Sar and MeAla, 6.5; Pro 14.5. On column B (3% Poly-A 103 on Gas Chrom Q, 100–120 mesh) at 80°, with a 4°/min temperature program, retention times were: MeAla, 5.7; Sar, 6.5; Val, 9.4; Pro, 13.3; Thr, not detected. Peak area ratio data from columns A and B in comparison with standard mixtures afforded molar ratios of amino acids present in hydrolysates.

Table III. Comparison of the Average Dimensions of the Ten Peptide Residues in the Present Structure with Literature Averages

	present work	Benedetti[30]
N(i+1)-C'(i)	1.341 (6) Å	1.335 Å
C'(i)-O(i)	1.227 (8) Å	1.229 Å
C'(i)-C^{α}(i)	1.528 (8) Å	1.522 Å
C^{α}(i)-N(i)	1.465 (8) Å	1.449 Å
N(i+1)-C'(i)-O(i)	121.8 (1.2)°	122.9°
N(i+1)-C'(i)-C^{α}(i)	118.4 (1.9)°	116.6°
O(i)-C'(i)-Cα(i)	119.7 (1.0)°	120.4°

Chemical ionization mass spectra (CIMS) were obtained on a Finnigan 1015 mass spectrometer.

Carbobenzoxy-D-valyl-L-proline (III). An ice-cold solution of carbobenzoxy-D-valine (15.00 g, 59.7 mmol) and L-proline methyl ester (7.74 g, 59.9 mmol) in chloroform (120 mL) was stirred during addition of dicyclohexylcarbodiimide (14.98 g, 72.6 mmol) in chloroform (50 mL) during 30 min. After 20 h at room temperature, acetic acid (2 mL) was added and the solution kept 30 min before filtration and evaporation. The residue, dissolved in ethyl acetate, was washed with 0.5 N hydrochloric acid, aqueous sodium bicarbonate, and aqueous sodium chloride, and then dried (Na_2SO_4) and evaporated. The residual oil (methyl ester of III) was subjected to CIMS (a) with methane [ions at m/z 363 (M + 1, relative intensity (r.i.) 1.00) and 391 (M + 29, relative intensity 0.069)] and (b) with ammonia [ions at m/z 363 (M + 1, relative intensity 1.00) and 380 (M + 18, relative intensity 0.026)], indicating M = 362 ($C_{19}H_{26}N_2O_5$ requires 362.184). This product was dissolved in ethanol (100 mL) and cooled in ice, and 1 N sodium hydroxide (75 mL) was added. After 20 h at room temperature, the solution was concentrated, diluted with water (200 mL), washed with ethyl acetate, adjusted to pH 2.5 with hydrochloric acid and extracted with ethyl acetate. The extracts were washed with aqueous sodium chloride, dried over sodium sulfate, and evaporated to afford III as an oil, yield 19.15 g (92%). The crystalline (needles) dicyclohexylammonium salt had mp 154.5–156 °C. Anal. Calcd for $C_{30}H_{47}N_3O_5$: C, 67.94; H, 9.10; N, 7.93. Found: C, 68.02; H, 8.94; N, 7.93.

Carbobenzoxy-D-valyl-L-prolylsarcosine Methyl Ester (IV). A solution of III (11.13 g, 31.9 mmol) in acetonitrile (150 mL) containing triethylamine (5.4 mL) was stirred and cooled to −5 °C during addition of isobutyl chloroformate (3.8 mL). After 15 min, a mixture of sarcosine methyl ester hydrochloride (4.24 g, 30.4 mmol) and triethylamine (4.5 mL) in acetonitrile (25 mL) was added. After 1 h at −5 °C, and 20 h at room temperature, the mixture was filtered and evaporated. The residue, dissolved in ethyl acetate, was washed with 0.5 N hydrochloric acid, aqueous sodium bicarbonate, and aqueous sodium chloride, dried (Na_2SO_4), and evaporated to afford IV as a gum (yield 8.41 g, 64%). CIMS (a) with methane [ions at m/z 434 (M + 1, relative intensity 1.00) and 462 (M + 29, relative intensity 0.20)] and (b) with ammonia [ions at m/z 434 (M + 1, relative intensity 1.00) and 451 (M + 18, relative intensity 0.15)] indicated M = 433 ($C_{22}H_{31}N_3O_6$ requires M = 433.22). Amino acid analysis: Val, 1.05; Pro, 0.93; Sar, 1.02.

***N-tert*-Butoxycarbonyl-*O*-benzyl-L-threonyl-D-valyl-L-prolylsarcosine Methyl Ester (V).** *N-tert*-Butoxycarbonyl-*O*-benzyl-L-threonine (7.02 g, 22.7 mmol) in acetonitrile (100 mL) containing triethylamine (5.0 mL) was stirred and cooled to −5 °C, and isobutyl chloroformate (3.0 mL) was added. After 15 min, a solution of D-valyl-L-prolylsarcosine methyl ester (from hydrogenation of IV (9.70 g, 22.4 mmol) in ethyl acetate over 10% palladium/charcoal) was added and the mixture was stirred for 1 h at −5 °C. After 16 h at room temperature the solution was filtered and evaporated. The residue, dissolved in ethyl acetate, was washed with 0.5 N hydrochloric acid, aqueous sodium bicarbonate, and aqueous sodium chloride, dried (Na_2SO_4), and evaporated. The residue was chromatographed on a column (30 × 4.8 cm) of alumina (neutral, Brockmann activity I) in ethyl acetate/chloroform (2:1) to afford V as an amorphous solid (yield 10.7 g, 81%), which crystallized from ethyl acetate/petroleum ether as needles, mp 84–87 °C. Anal. Calcd for $C_{30}H_{46}N_4O_8$: C, 61.00; H, 7.85; N, 9.49. Found: C, 61.44; H, 8.17; N, 9.11. Amino acid analysis: Thr, 0.87; Val, 1.03; Pro, 1.00; Sar, 1.11.

***N-tert*-Butoxycarbonyl-*N*-methyl-L-alanyl-*O*-benzyl-L-threonyl-D-valyl-L-prolylsarcosine Methyl Ester (VI).** A solution of V (8.92 g, 15.1 mmol) in 4 N hydrogen chloride/dioxane (50 mL) was kept at room temperature for 30 min, then evaporated in vacuo. The residue, dissolved in methanol (200 mL), was stirred for 3 h with a weakly basic anion-exchange resin (Rexyn 203, 70 g). After the resin was removed by filtration the solution was evaporated in vacuo to afford the tetrapeptide methyl ester as a gum. Meanwhile, a solution of *N-tert*-butoxycarbonyl-*N*-methyl-L-alanine (3.80 g, 18.7 mmol) and triethylamine (3.5

mL) in acetonitrile (70 mL) was stirred at −10 °C during addition of isobutyl chloroformate (2.0 mL). After 15 min, a cooled solution of the above tetrapeptide methyl ester (6.98 g, 14.2 mmol) in acetonitrile (60 mL) was added. After 1 h at −10 °C and 16 h at room temperature, the solution was filtered and evaporated. The residue, dissolved in ethyl acetate, was washed with 0.5 N hydrochloric acid, aqueous sodium bicarbonate, and aqueous sodium chloride, dried (Na_2SO_4), and evaporated to afford VI as a gum (yield, 7.02 g, 73%). Amino acid analysis: MeAla, 1.07; Thr, 0.86; Val, 1.04; Pro, 0.99; Sar, 1.04.

***cyclo*-(*O*-Benzyl-L-threonyl-D-valyl-L-prolylsarcosyl-*N*-methyl-L-alanyl) (II).** A solution of VI (9.35 g, 13.8 mmol) in methanol (90 mL) was cooled in ice and 1 N sodium hydroxide (25 mL) was added. After 3 h at 0 °C and 20 h at room temperature, the solution was concentrated, diluted with water (300 mL), washed with ethyl acetate, acidified with citric acid (6 g), and extracted with ethyl acetate. The extracts were washed with aqueous sodium chloride, dried (Na_2SO_4), and evaporated to afford the *tert*-butoxycarbonyl pentapeptide as an amorphous solid (yield, 8.98 g, 98%) which was used directly for the next step. An aliquot (2.59 g, 3.91 mmol) was dissolved in 4 N hydrogen chloride/dioxane (15 mL) and kept at room temperature for 30 min. After evaporation in vacuo, the residual deprotected pentapeptide hydrochloride was dissolved in methylene chloride (4.5 L) and diisopropylethylamine (1.25 mL) was added, followed by 1-hydroxybenzotriazole monohydrate (0.6 g) and dicyclohexylcarbodiimide (4.03 g, 19.4 mmol). After 5 days at room temperature, acetic acid (2.5 mL) was added. After 30 min the solution was evaporated and the residue dissolved in ethyl acetate (300 mL). The solution was washed with 0.5 N hydrochloric acid, aqueous sodium bicarbonate, and aqueous sodium chloride, dried (Na_2SO_4), and evaporated. The residue was dissolved in benzene and applied to a column (18 × 1.8 cm) of acid-washed alumina. After the passage of benzene (100 mL) through the column, the product was eluted with ethyl acetate. Evaporation afforded II was a crystalline solid (yield 656 mg, 31%) which recrystallized from ethyl acetate as needles, mp 199–201 °C. Anal. Calcd for $C_{28}H_{41}N_5O_6$: C, 61.86; H, 7.60; N, 12.88. Found: C, 61.86; H, 7.65; N, 12.87. CIMS with methane [ions at m/z 544 (M + 1, relative intensity 1.00) and 572 (M + 29, relative intensity 0.10)] indicated M = 543 (required, 543.304). Amino acid analysis: Thr, 0.80; Val, 1.06; Pro, 0.95; Sar, 1.09; MeAla, 1.10.

***cyclo*-(L-Threonyl-D-valyl-L-prolylsarcosyl-*N*-methyl-L-alanyl) (I).** A solution of II (479 mg, 0.88 mmol) in methanol (10 mL) was hydrogenated over 5% palladium/charcoal at atmospheric pressure and temperature for 20 h. After filtration and evaporation, I was obtained as an amorphous solid (yield 396 mg, 99%). CIMS with methane [ions at m/z 454 (M + 1, relative intensity 1.00) and 482 (M + 29, relative intensity 0.068)] indicated M = 453 ($C_{21}H_{35}N_5O_6$ requires M = 453.274). Amino acid analysis: Thr, 0.86, Val, 1.01; Pro, 0.96; Sar, 1.06; MeAla, 1.12.

Proton NMR spectra of I and II in various solvents (Table I) were obtained on a Varian HR220 in the CW mode. A spectrum of II in $CDCl_3$ was also obtained at 600 MHz (Mellon Institute) in the correlation mode (Figure 2). Assignments were aided by track-field decoupling experments. Thus, in the case of II in $CDCl_3$ at 220 MHz, irradiation at 465 Hz collapsed the methyl doublets at δ 0.88 and 0.93 to singlets and the α-proton doublet of doublets at δ 4.39 to a doublet. Irradiation at the frequency of the latter collapsed the NH doublet at δ 6.20 to a singlet. All the above signals are therefore identifiable with valine, the original irradiation being at the frequency of its β proton. Likewise, the other NH doublet at δ 7.48 was related to the doublet of doublets at δ 4.74; the latter threfore belongs to the threonine α proton. The quartet at δ 5.47 was clearly the *N*-methylalanine α proton, since irradiation at its frequency collapsed the methyl doublet at δ 1.44 to a singlet. The remaining methyl doublet at δ 1.13 must therefore belong to threonine, and the related β proton was located when this doublet collapsed upon irradiation at 4.57 ppm. This procedure also collapsed the doublet at δ 3.15, and since the latter has a geminal coupling constant, and therefore belongs to sarcosine, it is apparent that the threonine β proton overlaps the other sarcosine α proton (and the benzylic CH_2 protons) in the region of δ 4.6 (this overlap persists at 600 MHz). The only remaining α-proton signal at δ 4.95 must belong to proline; this doublet of doublets collapses upon irradiation at 2.16 or 1.75 ppm, thus identifying the locations of the two β protons. Coupling constants (Hz) were as follows: Thr NH,CαH, 9.8; Val NH,CαH, 10.0; Thr α,β, 1.2; Val α,β, 10.0; Sar α,α, 14.5; Pro α,β, 4.4 and 9.2; Thr β,Me 6.6; Val β,Me 6.5; MeAla α,Me 7.8.

C-13 NMR spectra of II in $CDCl_3$ were obtained on a JEOL FX60 spectrometer at 15 MHz, and on the NIH hybrid spectrometer at 67 MHz. Typically, 10 000 free induction decays were obtained on a 0.02 M solution.

The α-carbon atoms of the amino acids can be securely identified by single-proton decoupling experiments (SPSD) and single-frequency off-resonance (SFOR). The former technique allowed secure identification of the α carbons of *N*-methylalanine, proline, threonine, and valine by irradiation at proton frequencies corresponding to 5.47, 4.95, 4.74, and 4.39 ppm. At high field, the α-methylene of sarcosine appeared as a characteristic doublet of doublets because of the marked difference in chemical shifts of the two protons. The β and benzylic protons of the *O*-benzylthreonine residue are readily recognized by their characteristic chemical shift and SFORD experiments, and the β carbon of valine by SFPD. The methyl groups of *N*-methylalanine and of valine (as a pair) were identified by SFPD, leaving the signal at 17.7 ppm to be recognized by elimination and SFORD as that of threonine. As no specific decoupling experiments identified the methylene groups of the proline residue, the assignments correspond to the chemical shifts anticipated from earlier observations.

Table IV. Crystal and Experimental Data

molecular formula: $C_{28}H_{41}N_5O_6$
molecular weight: 543.66
radiation: Cu Kα (graphite monochromator)
wavelength: 1.5418 Å
space group: $P2_1$ (no. 4)
cell dimensions (from least-squares ref of $\pm\theta$ data)
a = 10.167 (1) Å b = 28.047 (2) Å
c = 10.581 (1) Å β = 106.39 (1)°
V = 2894.60 Å^3 Z = 4
D_{obsd} = 1.26 (1) g cm^{-3} D_{calcd} = 1.267 g cm^{-3}
crystal size: 0.3 × 0.2 × 0.2 mm^3: prismatic
maximum sin θ/λ = 0.61 Å^{-1}
theoretical resolution of data: 0.5 Å
diffractometer: Nonius CAD-4
least-squares weighting: after S. W. Peterson and H. A. Levy, *Acta Crystallogr.*, **10**, 70 (1957)
function minimized: $\Sigma w\Delta^2$
anisotropic temperature factor: $\exp(-2\pi^2(\Sigma_i\Sigma_j U_{ij}a^*_i a^*_j h_i h_j))$
final R factor (4992 reflections: 2σ): 3.7%

X-ray Crystallography. The basic crystal and data collection details are given in Table IV. Data collection techniques involved $\theta/2\theta$ scans, and standard reflections, measured periodically, showed no evidence of significant radiation damage. The crystals contain no solvent of crystallization and are stable in air. Only those reflections with $I > 2\sigma(I)$ were used in the final least-squares refinement. All reflections were measured using a maximum time of 120 s. Lorentz and polarization corrections were applied to the data but no absorption corrections were made.

The phase problem was solved using MULTAN 78[36] but not completely automatically. Automatic runs using the convergence mapping procedure of MULTAN 78 invariably led to *E* maps with one superlarge peak for "solutions" with the best figures of merit. Some inspection was done of other solutions possessing at least one good figure of merit but no promising molecular fragments were found. An analysis of the process of phase determination indicated that several planes of large *E* value had less than the average number of phase equations and were not evaluated until very late in the procedure. Four such planes of large *E* value were thus assigned as variables and five others were also added which showed early interaction with them. Two Σ_1 assignments, of fairly high probability if the whole data set was used instead of the limited set of MULTAN 78, were also added as known phases with 50% weighting. The rather large set of variable phases was practicable because of the "magic integer" technique incorporated in the program. Inspection of the results of an *E* map calculation showed all but three of the heavier atoms expected and no chemically reasonable false peaks. The *E* map indicated two separate, very similar molecules with any peaks apparently connecting the molecules being of very much lower density than those which were actually assigned to atoms.

Subsequent refinement was done by standard techniques using the programs of XRAY.[37] At the point where anisotropic thermal refinement was applied to the heavier atoms, it became apparent that the thermal parameters for C$^\gamma$ of the proline ring of the first molecule were so large as to be physically unreasonable. The rms amplitudes of vibration suggested that the atom could be represented by two half-atoms separated by a distance greater than the resolution of the data. The model refined without problems and the thermal parameters for the half-atoms became almost isotropic. Conformational disorder of proline rings has been

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reported quite frequently in crystal structure determinations; e.g., there are two examples of such disorder in 1979 alone.[12,38]

It would have been desirable to treat the adjacent atoms similarly but the corresponding positions would be below the limit of the resolution. Except for those attached to C^{γ} (proline) of the first molecule, evidence was found for all hydrogen atoms in a difference map. Hydrogen atom positions were calculated for those of the two C^{γ} sites. Final refinement utilized anisotropic thermal parameters for all heavier atoms and isotropic parameters for hydrogen atoms. All parameters, except for the thermal parameters of the hydrogen atom involved in the disorder, were refined. It was assumed that the population parameters for all disordered sites were 0.5 and no refinement was attempted. The final R factor was 3.7%; final parameters for the heavier atoms and for the hydrogen atoms are given as supplementary material. The refinement was carried out by full-matrix least-squares techniques although the structure was partitioned into many groups of atoms because of computer size limitations. No evidence of unexplained density was apparent in a final difference map. A table of observed and calculated structure factors has been also deposited. (See paragraph at end of paper concerning supplementary material.)

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Registry No. I, 76805-10-2; II, 76805-09-9; III, 47450-18-0; III methyl ester, 51782-77-5; III dicyclohexylammonium salt, 27483-24-5; IV, 79663-88-0; V, 79663-89-1; VI, 79663-90-4; carbobenzoxy-D-valine, 1685-33-2; L-proline methyl ester, 2577-48-2; D-valyl-L-prolylsarcosine, 79663-91-5; *N-tert*-butoxycarbonyl-*O*-benzyl-L-threonine, 15260-10-3; *N-tert*-butoxycarbonyl-*N*-methyl-L-alanine, 16948-16-6; *O*-benzyl-L-threonyl-D-valyl-L-prolylsarcosine methyl ester, 79663-92-6; *N-tert*-butoxycarbonyl-*N*-methyl-L-alanyl-*O*-benzyl-L-threonyl-D-valyl-L-prolylsarcosine, 79663-93-7.

Supplementary Material Available: A table of observed and calculated structure factors, table of benzyl dimensions, table of positional and thermal parameters for the heavier atoms, table of parameters for hydrogen atoms and a stereopacking diagram (33 pages). See current masthead page for ordering information.

Asymmetric Synthesis Catalyzed by Chiral Ferrocenylphosphine–Transition Metal Complexes. 2.[1] Nickel- and Palladium-Catalyzed Asymmetric Grignard Cross-Coupling[2]

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Abstract: Various kinds of chiral ferrocenylphosphines, which have both planar and central elements of chirality and also a functional group on the side chain, have been used as ligands for nickel or palladium complex catalyzed asymmetric cross-coupling of secondary alkyl (1-phenylethyl, 2-octyl, and 2-butyl) Grignard reagents with organic halides such as vinyl bromide, (*E*)-β-bromostyrene, 2-bromopropene, and bromobenzene. (*S*)-*N*,*N*-Dimethyl-1-[(*R*)-2-(diphenylphosphino)ferrocenyl]ethylamine [(*S*)-(*R*)-PPFA] was one of the most effective ligands giving the coupling product, 3-phenyl-1-butene, of up to 68% ee in the reaction of 1-phenylethylmagnesium chloride with vinyl bromide, and it was found that the ferrocene planar chirality is more important than the carbon central chirality and the dimethylamino group is the first requisite for the high stereoselectivity. The stereoselectivity was not affected by introduction of substituents onto the diphenylphosphino group of the ligand, but was strongly affected by changing the steric bulkiness of the secondary amino group on the ferrocenylphosphine side chain. A mechanism, where the coordination of the amino group on the ligand with the magnesium atom in the Grignard reagent plays a key role in a diastereomeric transition state, is proposed to account for the ferrocenylphosphine ligands causing a high asymmetric induction.

Asymmetric synthesis catalyzed by chiral transition metal complexes has been intensively studied in the last several years and is now recognized to be a promising method for the synthesis of optically active compounds. One of the most crucial points in obtaining high stereoselectivity in the catalytic asymmetric synthesis is the choice of the ligand which will fit in with a given reaction as efficiently in stereoselectivity as possible. In the asymmetric hydrogenation of α-acylaminoacrylic acids catalyzed by chiral rhodium complexes, over 90% optical yields have been achieved[4] and the dependence of the stereoselectivity on structural

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