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STRUCTURAL REQUIREMENTS IN CHIRAL DIPHOSPHINE-RHODIUM COMPLEXES—XII[1]

ASYMMETRIC HOMOGENEOUS HYDROGENATION OF Z-α-N-METHYLACETAMIDOCINNAMIC ACID AND METHYL ESTER CATALYZED BY RHODIUM(I) COMPLEXES OF DIOP AND ITS CARBOCYCLIC ANALOGUES

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Abstract—Z-α-N-methylacetamidocinnamic acid and its methyl ester were hydrogenated with rhodium(I) complexes containing (2*R*, 3*R*)-O-2,3-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane (DIOP) or its carbocyclic analogues: (1*R*, 2*R*)-*trans*-1,2-bis(diphenylphosphinomethyl)cyclobutane or (1*S*, 2*S*)-*trans*-1,2-bis(diphenylphosphinomethyl)cyclohexane. The N-acetyl-N-methylphenylalanine methyl ester reaction product was formed with an optical purity of 73% ee-(*R*) [(2*R*, 3*R*)-DIOP]; 43% ee-(*R*) [(1*R*, 2*R*)-cyclobutane analogue]; and 26% ee-(*R*) [(1*S*, 2*S*)-cyclohexane analogue]. Similarly, N-acetyl-N-methylphenylalanine was formed with an optical purity of 87% ee-(*R*) [(2*R*, 3*R*)-DIOP] and 68% ee-(*R*) [(1*R*, 2*R*)-cyclobutane analogue].

The state of the art in asymmetric hydrogenation using rhodium(I) complexes of chiral diphosphines has progressed to the point where reaction products have been obtained showing approximately 100% optical purity.[2] The high degree of enantioface selectivity exhibited by these Rh(I)/chiral diphosphine complexes in the hydrogenation of prochiral dehydroamino acid derivatives may be likened in some respects to the intimate relationship found between a "lock" and a "key". To a certain extent, it even is not altogether unreasonable to consider such complexes to be enzyme analogues. In this particular case, the chiral diphosphine/Rh(I) complex may be considered to be the "lock" while the prochiral substrate [the dehydroamino acid derivative] is designated as the "key". We have been investigating these types of interactions in which the polar/electronic and steric factors may be metaphorically thought of as the "tumblers of the lock" or the "indentations of the key".

Some systematic investigations of structural parameters in the "key" (such as changes in the carboxyl[1,3,4] and acylamino[1,5,6] moieties as well as in the β-substituent[7]) have recently been undertaken. In such systematic studies [based upon increasing the steric bulk of a particular moiety in the prochiral substrate] insight into polar/electronic effects can be obtained in addition to the obvious steric factors. Meaningful deviations in the behavior of a particular member of a series [for example, CF_3 in the series: Me, CF_3, t-Bu] can provide useful information regarding the existence of the above-mentioned polar/electronic effects within the active catalytic species.[1,5]

Concurrently with these systematic investigations of the "key", we have started to undertake similar studies of the "lock". Chiral carbocyclic analogues of the heterocyclic diphosphine: (2*R*, 3*R*)-O-2,3-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane[8] (DIOP) (I) have been synthesized.[1,4,7,9–11] In these chiral *trans*-1,2-bis(diphenylphosphinomethyl)cycloalkanes (II–III), the torsional angle is varied between the two diphenylphosphinomethyl [Ph_2PCH_2-] ring substituents (see Fig. 1).†

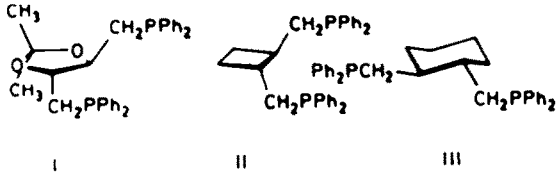

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Fig. 1.

We are interested in studying the sensitivity to steric change [in the prochiral substrates] felt by the active catalytic species containing these carbocyclic DIOP analogues.

RESULTS AND DISCUSSION

This current work describes the effect of N-methylation in the prochiral substrate upon the degree of enantioface selectivity exhibited by the chiral hydrogenation catalysts.

Z-methyl-α-N-methylacetamidocinnamate (IV) was

†The possible implications of this torsional angle upon the optical purity of the products were discussed in our earlier work.[7] In that work, the model compound *trans*-1,2-cyclopentane dicarboxylic acid mono N-methyl amide is in error, and all reference to it should be disregarded.

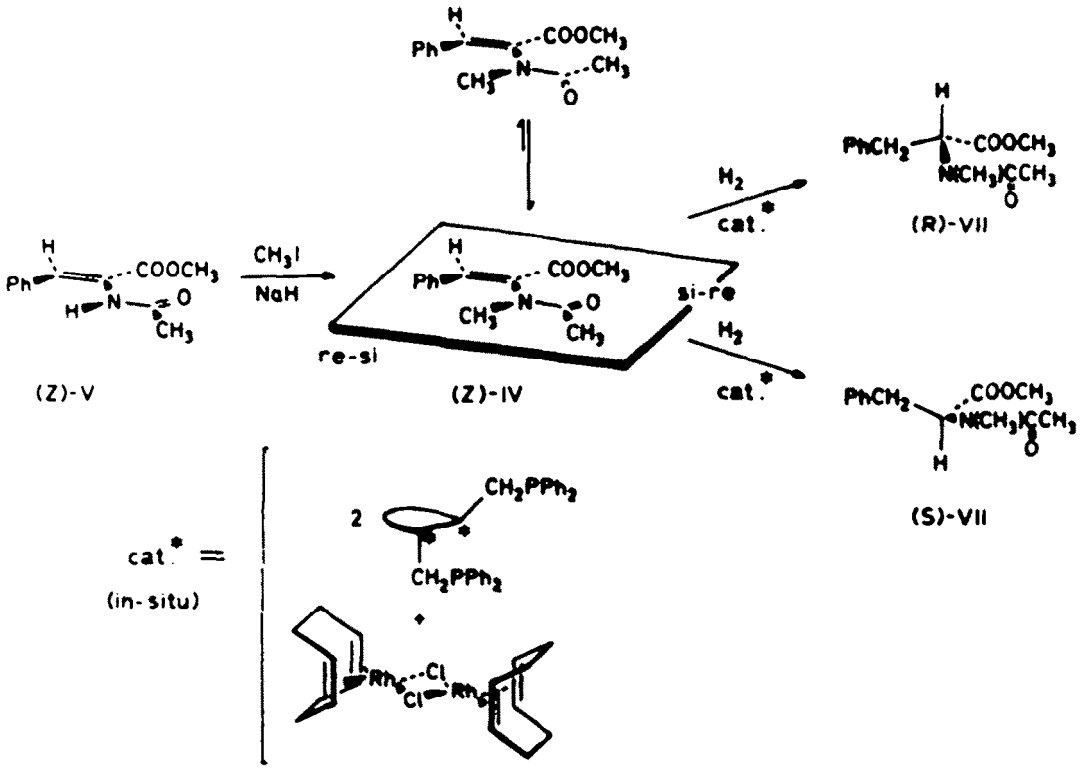
prepared from Z-methyl-α-acetamidocinnamate (V) using methyl iodide and sodium hydride (see Scheme 1). Mild KOH catalyzed hydrolysis of the unsaturated ester IV afforded the Z-α-N-methylacetamidocinnamic acid (VI). The ^{1}H NMR spectra of both the N-methylated dehydroamino acid VI and methyl ester IV show the presence of *trans* and *cis*-amide conformers in $CDCl_3$/TMS solution. In both unsaturated substrates IV and VI, the *trans*/*cis*-amide conformers are present in the ratio of approximately 88/12.

The ^{1}H NMR signals (in $CDCl_3$/TMS) of the $CH_3C{=}O$ protons for the major and minor amide conformers of methyl ester IV appear at 1.87 and 2.21 δ, respectively [while in the free acid VI they appear now at 1.98 and 2.29 δ, respectively]. The amide conformeric ratio in the unsaturated methyl ester IV did not vary when the solvent was changed to trifluoroacetic acid (TFA). LaPlanche and Rogers have studied the ^{1}H NMR spectra of unsymmetrically N,N-disubstituted amides.[12] It was found that in the preferred isomer, the bulkier substituent on nitrogen is *trans* to the acetyl Me group of acetamides.[12] Thus, the major amide conformer in both the methyl ester IV and in the free acid VI has been assigned the *trans*-amide conformation (Fig. 2). The non-N-methylated unsaturated ester, Z-methyl-α-acetamidocinnamate (V) exhibits ^{1}H NMR signals of only the *trans*-amide conformer in $CDCl_3$. Change of solvent to TFA results in a *trans*/*cis*-amide ratio of 80/20 for this substrate.

Fig. 2.

The two N-methylated prochiral substrates IV and VI underwent asymmetric hydrogenation (in abs ethanol/benzene 2.3:1) catalyzed by Rh(I) complexes containing chiral *trans*-1,2-bis(diphenylphosphinomethyl)cycloalkanes (II–III) and DIOP (I). N-methylation had a great influence upon the rate of hydrogenation of these substrates. For example, while the half-life period for the hydrogenation of Z-methyl-α-acetamidocinnamate (V) catalyzed by a neutral Rh(I)/DIOP complex was found to be approximately 7 minutes [under the particular reaction conditions employed in all of these experiments],[13] the N-methylated analogue IV was reduced more slowly under the same conditions [only 73% chemical conversion was noted after 24 hr]. The corresponding N-methylated unsaturated free acid VI was even more slowly reduced [only 54% chemical conversion was noted after a 24 hr reaction period].

It is reasonable to expect that N-methylation would exert an influence upon the factors likely to effect the conformation of the unsaturated substrate and also those which effect the interaction of the olefin with the chiral catalytic hydrogenation complex. The results of the asymmetric hydrogenation experiments are given in Table 1. It can be seen that the N-acetyl-N-methylphenylalanine methyl ester (VII) reaction product was produced with an optical purity of 73% ee-(*R*) [(2*R*, 3*R*)-DIOP]; 43% ee-(*R*) [(1*R*, 2*R*)-cyclobutane analogue]; and 26% ee-(*R*) [(1*S*, 2*S*)-cyclohexane analogue]. These results can be compared with those obtained with the non-methylated analogue V: 69% ee-(*R*) [(2*R*, 3*R*)-



Scheme 1.

Table 1. Asymmetric hydrogenation of Z-methyl α-N-methylacetamidocinnamate (IV) and free acid (VI) catalyzed by neutral chlororhodium(I)/chiral diphosphine complexes[a]

Olefin	Diphosphine	% Conv.[b]	$[\alpha]_D^{25}$,[c]	% Opt. purity[d]	Abs. config.
IV	(2*R*, 3*R*)-I[e]	73	+45.7	73	R
IV	(1*R*, 2*R*)-II[f]	92	+26.7	43	R
IV	(1*S*, 2*S*)-III[g]	59	+16.5	26	R
VI	(2*R*, 3*R*)-I[e]	54	+54.2	87	R
VI	(1*R*, 2*R*)-II[f]	~100	+42.7	68	R
VI	(1*S*, 2*S*)-III[g]	15	—[h]	—	—

[a][Rh] = 3.0 mmol l^{-1}; [diphosphine]/[Rh] = 1.1; [substrate]/[Rh] = 25; [abs. EtOH]/[benzene] = 2.3; total volume 10 ml; 1 atm. H_2; and 25°C. [b]Determined by gas chromatography. [c]$10^{-1} \times [\alpha]$ = degree g^{-1} cm^2; (C, 1.0, $CHCl_3$). [d]Based upon N-acetyl-N-methyl-(*S*)-phenylalanine methyl ester: $[\alpha]_D^{25} - 62.5°$ (C, 1.0, $CHCl_3$); free acid reduction products converted to methyl esters via diazomethane prior to determination of optical purity. [e](2*R*, 3*R*) - O - 2,3 - isopropylidene - 2,3 - dihydroxy - 1,4 - bis(diphenylphosphino)butane (DIOP). [f](1*R*, 2*R*) - trans - 1,2 - bis(diphenylphosphinomethyl)cyclobutane. [g](1*S*, 2*S*) - trans - 1,2 - bis(diphenylphosphinomethyl)cyclohexane. [h]Optical rotation not determined due to low chemical conversion.

DIOP];[3] 44% ee-(*R*) [(1*R*, 2*R*)-cyclobutane analogue];[4] and 1% ee-(*R*) [(1*S*, 2*S*)-cyclohexane analogue].[1]

Similarly, N-acetyl-N-methylphenylalanine free acid (VIII) was formed with an optical purity of 87% ee-(*R*) [(2*R*, 3*R*)-DIOP]; and 68% ee-(*R*) [(1*S*, 2*S*)-cyclobutane analogue]. When the catalyst used was the rhodium(I)/(1*S*, 2*S*) - *trans* - 1,2 - bis(diphenylphosphinomethyl)cyclohexane complex, the saturated reaction product was produced in only 15% chemical conversion after a 24 hr reaction period. Therefore, the low quantity of unsaturated product did not permit the determination of product optical purity in this case. The non-methylated free acid analogue (Z-α-acetamidocinnamic acid) gave a reduction product optical purity of 82% ee-(*R*) [(2*R*, 3*R*)-DIOP];[3] and 86% ee-(*R*) [(1*R*, 2*R*)-cyclobutane analogue].[7]

It is seen that the presence of the N-Me moiety did not significantly effect the optical purity of the methyl ester product (73% ee-(*R*) [N-Me] vs 69% ee-(*R*) [N–H]) or the free acid product (87% ee-(*R*) [N-Me] vs 82% ee-(*R*) [N–H]) when the catalytic system employed was the rhodium(I)/DIOP complex. Similarly, the presence or absence of N-methylation did not effect the optical purity of the methyl ester product (43% ee-(*R*) [N-Me] vs 44% ee-(*R*) [N–H]) when the neutral Rh(I)/(1*R*, 2*R*)-cyclobutane analogue II was utilized. However, with the latter catalytic system N-methylation of the unsaturated free acid VI resulted in a decrease in attack upon the si-re prochiral face to give less of the (*R*)-amino acid derivative: 68% ee-(*R*) [N-Me] vs 86% ee-(*R*) [N–H]. Finally, it is seen that N-methylation resulted in a fairly large change in the optical purity of the methyl ester product (26% ee-(*R*) [N-Me] vs 1% ee-(*R*) [N–H]) when the neutral Rh(I)/(1*S*, 2*S*)-cyclohexane analogue III was utilized. If we correct for the (1*S*, 2*S*)-chirality of the cyclohexane diphosphine utilized [vs the (*R*, *R*)-chirality of DIOP and its cyclobutane analogue II], it is seen that N-methylation again resulted in a decrease in attack upon the si-re prochiral face. The higher sensitivity of the Rh(I)/cyclohexane analogue III hydrogenation complex to increasing steric bulk within the alcohol moiety of Z-α-acetamidocinnamate esters [when compared to the two other above-mentioned chiral diphosphines I–II] has been interpreted in terms of a relatively more flexible 7-membered chelate ring between the diphosphine ligand and rhodium.[1] The greater sensitivity of this hydrogenation complex to N-methylation in the unsaturated methyl ester IV is consistent with this interpretation.

Other than the obvious conclusion that the amide proton does not appear to play an essential role in the enantioface differentiation process, a more detailed explanation of these experimental results is difficult at this stage. Additional studies of N-alkylation will have to be made before a more general assessment can be given about its behavior.

During the period that our work was in progress, a report appeared of the asymmetric hydrogenation of Z-α-N-methylbenzamidocinnamic acid using a cationic catalyst precursor, cyclooctadiene - 1,5[((*R*, *R*) - 1,2 - ethandiylbis(*o* - methoxyphenyl)phenylphosphine]-rhodium tetrafluoroborate.[14] While no details were given of the analytical procedure utilized to obtain the product optical purity, it was stated that the N-methylated product showed 68% ee-(*S*) vs 78% ee-(*S*) for the non-N-methylated analogue. Since this catalyst system involves a cationic Rh(I) hydrogenation complex (containing a 5-membered chelate ring with the chiral diphosphine), a direct comparison of these results with ours is not possible.

Finally, we would like to comment upon the ^{1}H NMR spectrum of the N-acetyl-N-methyl-(*S*)-phenylalanine methyl ester (VII) optically-pure standard listed in Table 2. Similar to the case of the dehydro precursor IV, it was found that signals corresponding to *cis*/*trans*-amide conformers were also present in the ^{1}H NMR spectrum of this material (Fig. 3, where R = $PhCH_2(CH_3OOC)CH$–). The major amide conformer shows N-methyl and N-methine signals at 2.74 δ (S) and 5.13 δ (D of D), respectively [in $CDCl_3$/TMS]. The major and minor amide conformers were found to be present in the ratio of 3/1 [in $CDCl_3$/TMS].

The ^{1}H NMR of disubstituted amides has been extensively studied.[15] In dimethylformamide, the N-Me ^{1}H NMR signal that is found at higher field (closer to TMS) has been assigned to be that arising from the Me group *cis* to the O atom. Initially, this assignment was based upon the larger long range coupling constant exhibited by this N-Me group relative to that shown by the lower field signal.[16] This large long range coupling constant was assumed to be that which arose from a *trans* geometrical relationship between the protons in the Me group and the aldehydic proton.[16] This assignment was later confirmed using NOE data.[17]

The ^{1}H NMR data of the N-acetyl-N-methyl-(*S*)-phenylalanine methyl ester (VII) [$RCH(NCH_3COCH_3)COOCH_3$, where R = $PhCH_2$] may be compared with those given for the known glycine [where R = H][18] and alanine [where R = CH_3][19] analogues. The ^{1}H NMR spectra for both the glycine [DMSO-d_6 solvent] and the alanine [CH_2Cl_2 solvent] analogues show the presence of *trans* and *cis*-amide conformations. In both cases, the major conformer was assigned the *trans*-amide conformation and exhibited the N-Me signal at lower field relative to the corresponding signal in the minor conformer.[18,19] As an initial starting point, this data would lead us to assign the *cis*-amide conformation to the major conformer of N-acetyl-N-methyl-(*S*)-phenylalanine methyl ester (VII) in $CDCl_3$.

Table 2. ^{1}H NMR of Z-methyl α-N-methylacetamidocinnamate (IV) and free acid (VI) [PhCH=C(NCH$_3$COCH$_3$)COOR where R = CH$_3$ or H, respectively] and N-acetyl-N-methyl-(*S*)-phenylalanine methyl ester (VII) [PhCH$_2$CH(NCH$_3$COCH$_3$)COOCH$_3$][a]

Compd.	Major conformer[b]		Minor conformer[c]		Major/minor
IV	7.54 (*S*)	1H–PhCH			7.3
	7.33 ± 0.15 (*M*)	5H–PhH$_5$	7.33 ± 0.15	5H–PhH$_5$	
	3.83 (*S*)	3H–CH$_3$O	3.78 (*S*)	3H–CH$_3$O	
	3.03 (*S*)	3H–CH$_3$N	3.03 (*S*)	3H–CH$_3$N	
	1.87 (*S*)	3H–CH$_3$C=O	2.21 (*S*)	3H–CH$_3$C=O	
VI	10.26 (broad *S*)	1H–COOH	10.26 (broad *S*)	1H–COOH	6.7
	7.66 (*S*)	1H–PhCH	7.18 (*S*)	1H–PhCH	
	7.38 ± 0.15 (*M*)	5H–PhH	7.38 ± 0.15 (*M*)	5H–PhH	
	3.10 (*S*)	3H–CH$_3$N	3.10 (*S*)	3H–CH$_3$N	
	1.98 (*S*)	3H–CH$_3$C=O	2.29 (*S*)	3H–CH$_3$C=O	
VII	7.10 ± 0.10 (*M*)	5H–PhH	7.10 ± 0.10 (*M*)	5H–PhH	3.3
	5.13 (*D* of *D*)	1H–CHN, J = 10.5 J = 5.5	4.51 (*D* of *D*)	1H–CH$_3$N, J = 10.5 J = 5.5	
	3.62 (*S*)	3H–CH$_3$O	3.67 (*S*)	3H–CH$_3$O	
	3.26 (*AB–Q*)	1H–CH$_2$C, J = 14 J = 5.5	—		
	3.00 (*AB–Q*)	1H–CH$_2$C, J = 14 J = 10.5	—		
	3.74 (*S*)	3H–CH$_3$N	2.81 (*S*)	3H–CH$_3$N	
	1.90 (*S*)	3H–CH$_3$C=O	1.70 (*S*)	3H–CH$_3$C=O	
VII[d]	7.03 ± 0.10 (*M*)	5H–PhH	7.03 ± 0.10 (*M*)	5H–PhH	3.0
	5.23 (*D* of *D*)	1H–CHN, J = 10.5 J = 5.5	4.33 (*D* of *D*)	1H–CHN, J = 10.5 J = 5.5	
	3.35 (*S*)	3H–CH$_3$O	3.32 (*S*)	3H–CH$_3$O	
	—[e]	1H–CH$_2$C	—		
	—[e]	1H–CH$_2$C	—		
	2.38 (*S*)	3H–CH$_3$N	2.80 (*S*)	3H–CH$_3$N	
	1.60 (*S*)	3H–CH$_3$C=O	1.60 (*S*)	3H–CH$_3$C=O	

[a]Spectra measured with a Varian XL-100-15 at 100 MHz, ambient probe temperature, chemical shifts are expressed in δ-values (ppm) relative to internal Me$_4$Si. *J* values are in Hz. Solvent is $CDCl_3$ except where otherwise noted. Multiplicities for the proton groupings are as follows: (*S*) = singlet, (*D* of *D*) = doublet of doublets, (*AB–Q*) = *AB* quartet, and (*M*) = multiplet. [b]Assigned the trans-amide structure. [c]Assigned the *cis*-amide structure. [d]Solvent is C_6D_6. [e]Two overlapping AB quartets.

However, such an assignment would be contrary to the finding (mentioned earlier) that the major isomer of unsymmetrical N,N-disubstituted acetamides is the *trans*-amide conformer based upon ^{1}H NMR [i.e. the bulkier substituent on the nitrogen is *trans* to the acetyl Me group in the preferred isomer].[12]

This seemingly paradoxical situation can be explained when the solvent effect of benzene (upon the ^{1}H NMR spectra of amides) is taken into consideration. In N-methyl-N-alkylamides (neat) it has been shown by ^{1}H NMR that the chemical shift of the N-Me group *trans* to the carbonyl oxygen (for the major conformer) is moved to higher field upon addition of benzene [while the corresponding signal in the minor *cis*-amide conformer is much less effected by the addition of benzene].[12] This phenomenon has been explained as arising from a specific interaction (Fig. 3a) between the benzene π-electrons and the N atom (which may be considered to bear a partial positive charge via resonance interaction with the adjacent CO moiety).[20] It has been proposed that in such an interaction, the partially negatively charged carbonyl oxygen atom would be as far away as possible from the center of the benzene ring.[20] CPK space-filling models show that the N-acetyl-N-methyl-(*S*)-phenylalanine methyl ester (VII) can assume a conformation (Fig. 3b) such that the phenyl group on the β-C atom can participate intramolecularly in a similar type of interaction with the amide N atom. Thus, this argument now allows us to assign the *trans*-amide structure to the major conformer of VII, even though the N-Me ^{1}H NMR signal appears at relatively higher field [in $CDCl_3$/TMS] than the corresponding signal in the minor conformer.

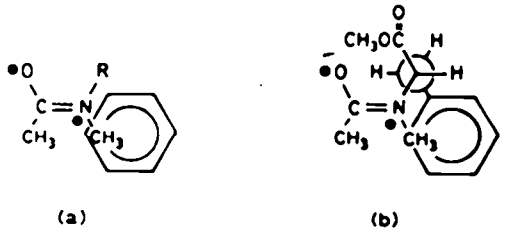


Fig. 3.

This new assignment is consistent with the ^{1}H NMR spectrum of VII that is obtained when C_6D_6/TMS is used as the solvent. Now, the N-Me signal of the major conformer appears at 2.38 δ while the corresponding signal in the minor conformer appears at 2.80 δ [compared to the corresponding signals at 2.74 and 2.81 δ, respectively when $CDCl_3$/TMS is the solvent].

Thus, in the three cases discussed above it appears that the steric and electronic nature of the group attached to the α-C atom in N-acetyl-N-methyl amino acid methyl esters [$RCH(NCH_3COCH_3)COOCH_3$, where R = H, CH_3 and CH_2Ph] does not alter the predominance of the *trans*-amide conformer relative to the *cis*-amide. However, the nature of this R group is shown to exert an influence upon the relative chemical shift values of the corresponding protons within the two amide conformer species.

EXPERIMENTAL

Hydrogenations were carried out in a glass atmospheric pressure apparatus at 25 ± 0.5° according to the method described.[3,21] Neutral rhodium(I) complexes were prepared from chloro(1,5-cyclooctadiene)rhodium(I) dimer [purchased from Strem Chemicals Inc.] according to the method described.[3,21] All m.ps are uncorrected. Microanalyses were performed at the Hebrew University of Jerusalem. ^1H NMR spectra were obtained on a Varian XL-100-15 spectrometer at 100.1 MHz.

(−)-(2*R*,3*R*)-DIOP, $[\alpha]_D^{22} - 11.9°$ (*c*, 1.0, benzene) lit.[22] $[\alpha]_D^{22} - 12.3°$ (*c*, 4.57, benzene), was purchased from Strem Chemicals Inc. and used as received. (1*R*,2*R*)-*trans*-1,2-bis(diphenylphosphinomethyl)cyclobutane, $[\alpha]_D^{20} - 17.0°$ (*c*, 1.0, benzene) and m.p. 107° lit.[11] $[\alpha]_D^{20} - 18.6°$ (*c*, 1.0, benzene) and m.p. 107°, was prepared according to the method of Rhone Poulenc S.A.[11] (1*S*,2*S*)-*trans*-1,2-bis(diphenylphosphinomethyl)cyclohexane, $[\alpha]_D^{25} + 52.7°$ (*c*, 1.0, benzene) and m.p. 55–56°, was prepared as described.[1]

Z-methyl α-N-methylacetamidocinnamate (*IV*). To 1.59 g (7.05 mmol) Z-methyl α-acetamidocinnamate (prepared as described,[3] dissolved in 50 ml dry THF, was added 339 mg (13.1 mmol) solid sodium hydride. Upon cessation of effervescence, 1.80 (28.2 mmol) MeI was added, the mixture stirred 2 days at room temp. and then evaporated *in vacuo* to dryness to yield a solid residue. The slurry produced after addition of 5 ml $CHCl_3$ was chromatographed on a silica-gel column (prepared in petroleum-ether 60–80°, and eluted with an increasing gradient of EtOAc in petroleum-ether 60–80°). A solid was obtained which after recrystallization from hot petroleum-ether 60–80° gave 0.80 g (49% yield) Z-methyl α-N-methylacetamidocinnamate, m.p. 55–57°. The IR spectrum (KBr pellet) showed absorptions at 1710 cm^{-1} (C=O stretch, ester), 1660 cm^{-1} (C=O stretch, amide), and 1620 cm^{-1} (C=C stretch). The ^1H NMR spectrum is listed in Table 2. (Found: C, 66.90; H, 6.70; N, 5.95. Calc. for $C_{13}H_{15}NO_3$: C, 66.95; H, 6.46; N, 6.00%).

Z-α-N-methylacetamidocinnamic acid (VI). To 1.25 g (5.37 mmol) Z-methyl α-N-methylacetamidocinnamate, dissolved in 15 ml THF, was added 4 ml 3N KOH and the mixture was stirred overnight at room temp. Upon cooling to 0°, 10 ml CCl_4, and 1.5 ml conc HCl were added. After evaporation *in vacuo* to dryness, the residue was partitioned between $CHCl_3$/water, and the aqueous layer extracted with $CHCl_3$. The combined organic layers were dried over $MgSO_4$, filtered, and evaporated *in vacuo* to dryness to yield a solid. Recrystallization for EtOAc/petroleum-ether 60–80° gave 0.80 g (68% yield) Z-α-N-methylacetamidocinnamic acid, m.p. 166–167°. The IR spectrum (KBr pellet) showed absorptions at 3050 cm^{-1} (O–H stretch, broad), 1710 cm^{-1} (C=O stretch, ester), and 1600 cm^{-1} (C=O stretch, amide and C=C stretch, broad). The ^1H NMR spectrum is listed in Table 2. (Found: C, 65.70; H, 6.08; N, 6.35. Calc. for $C_{12}H_{13}NO_3$: C, 65.75; H, 5.94; N, 6.40%).

N-Acetyl-N-methyl-(S)-phenylalanine methyl ester (VII). to 274 mg (1 mmol) N-methyl-(*S*)-phenylalanine methyl ester hydrobromide, $[\alpha]_D^{25} + 37.3°$ (*c*, 2, DMF) [prepared as described[23]], in 15 ml Na-dried benzene, was added 0.14 ml (1 mmol) Et_3N. After a second addition of 0.14 ml (1 mmol) Et_3N, 78.5 μl (1.1 mmol) acetyl chloride was added, the mixture stirred 1 hr at room temp. and then filtered. Upon evaporation of the filtrate to dryness *in vacuo*, an oil was obtained which was then chromatographed on a silica-gel column (prepared in petroleum-ether 60–80° and eluted with an increasing gradient of EtOH in petroleum-ether 60–80°) to give 200 mg (85% yield) N-acetyl-N-methyl-(*S*)-phenylalanine methyl ester as an oil; $[\alpha]_D^{25} - 62.5°$, $[\alpha]_{436}^{25} - 138.8°$, $[\alpha]_{334}^{25} - 329.0°$ (*c*, 1.0, $CHCl_3$). The IR spectrum (neat liquid between NaCl plates) showed absorptions at 1740 cm^{-1} (C=O stretch, ester); and 1650 cm^{-1} (C=O stretch, amide). The ^1H NMR spectrum is listed in Table 2. (Found: C, 66.12; H, 7.43; N, 6.07. Calc. for $C_{13}H_{17}NO_3$: C, 66.38; H, 7.23; N, 5.96%).

All reactions were terminated after 24 hr. After evaporation of the solvent *in vacuo*, the residues of crude product mixtures (from the free acid substrate) were directly treated with diazomethane in ether. The per cent conversion of all the esters (including those prepared via diazomethane) was determined by analysis on a Varian 2100 gas chromatograph as described.[1] All the crude esters were taken up in minimum quantity of $CHCl_3$ and chromatographed on a silica-gel column (prepared in petroleum-ether 60–80° and eluted with an increasing gradient of EtOAc in petroleum-ether 60–80°). The content of all fractions was determined by gas chromatography. Purified N-acetyl-N-methylphenylalanine methyl ester reaction products were stored in a desiccator *in vacuo* over P_2O_5 prior to determination of the optical rotation in a Perkin Elmer MC-141 polarimeter. The rotation was measured at three wavelengths: 589 (Na-D); 434.75 and 334.15 nm; 25° and a concentration of 1.0×10^{-2} g ml^{-1} in $CHCl_3$. The validity of the diazomethane treatment of crude free acid products has been shown.[1]

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