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STRUCTURAL REQUIREMENTS IN CHIRAL DIPHOSPHINE—RHODIUM COMPLEXES

IV *. USE OF *Z*-α-ACETAMIDOCINNAMATE ESTERS AS STRUCTURAL PROBES FOR DIOP—RHODIUM(I) COMPLEXES

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Summary

(—)-2,3-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane (DIOP) was used in neutral rhodium(I)—diphosphine complexes to catalyze the asymmetric hydrogenation of *Z*-α-acetamidocinnamate esters. Increasing the steric bulk of the alcohol moiety in the unsaturated esters resulted in enhancement of the optical purity in the *N*-acetylphenylalanine ester products without changing the chirality of the major product. In the series Me, Et, i-Pr and t-Bu, the optical purity increased from 69% ee (Me) to a maximum of 77% ee (t-Bu), while 1-adamantyl gave 71% of the *R*-isomer.

It has been shown that (+)- or (—)-2,3-isopropylidene-2,3-dihydroxy-1,4-bis-(diphenylphosphino)butane (DIOP) (I) [2,3] is an efficient chiral ligand when used in rhodium [1c,2—7] and ruthenium [8] catalyzed asymmetric hydrogenation reactions of amino-acid precursors. We decided to make a systematic study of the structural requisites in DIOP—rhodium hydrogenation complexes by utilizing unsaturated substrates with increasing steric bulk as topographical probes.

From the readily available *Z*-4-benzylidene-2-methyl-2-oxazolin-5-one (II) [1b,9], a series of *Z*-α-acetamidocinnamate esters (III) [1b] was synthesized by azlactone ring opening using the corresponding alkoxide [10]. A neutral rhodium(I) catalyst was prepared in situ from chloro(1,5-cyclooctadiene)-rhodium(I) dimer (IV) and (—)-DIOP (I) in benzene. This homogeneous catalyst was used in the asymmetric hydrogenation of the unsaturated esters, III, to the corresponding *N*-acetylphenylalanine esters (V) (see Scheme 1).

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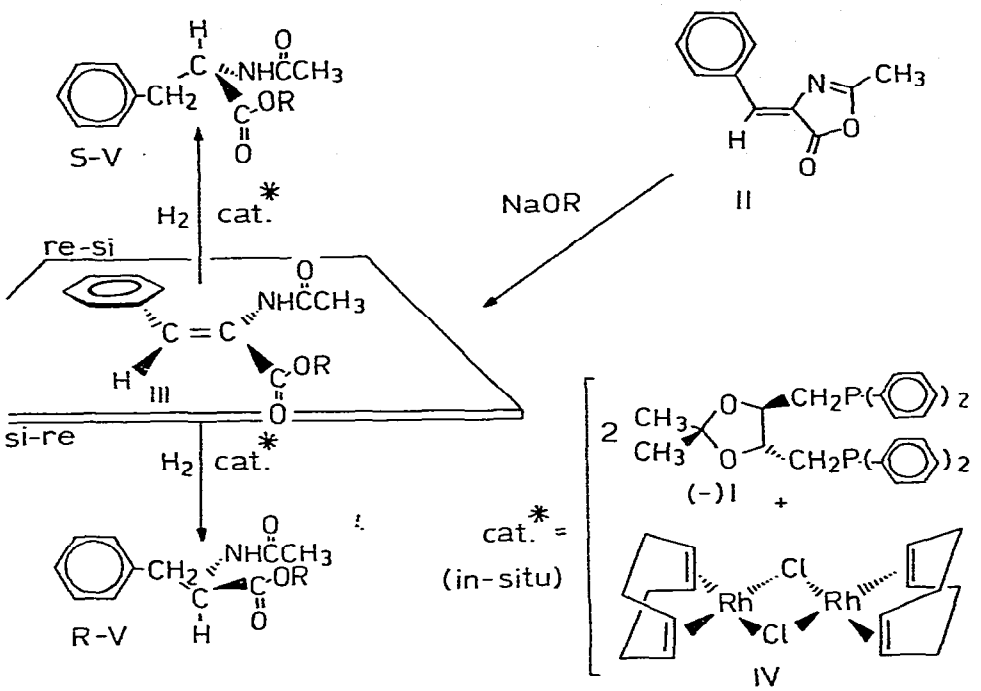
* For part I—III see ref. 1.

SCHEME 1.



Results and discussion

The question of *E,Z*-geometry within the unsaturated esters III has been unambiguously resolved by NMR [1b]. As for the α-benzamidocinnamic acids and esters [11,12], the stereochemistry of the acids and esters obtained by solvolysis of the stable azlactone (II) (prepared under basic conditions) was shown to be *Z*.

As shown in Table 1, the optical purity of the reaction products (reactions in 2.3 : 1.0 absolute ethanol/benzene mixtures) all fall within a fairly narrow range. Thus, the optical purity of the product undergoes small increments in the series: methyl (69% ee), ethyl (72% ee), i-propyl (76% ee) to a maximum with t-butyl (77% ee), and then suffers a decrease to 1-adamantyl (71% ee). Therefore, for the ester hydrogenation reaction as a whole, the product optical purity shows only slight sensitivity to increasing steric bulk in the alcohol moiety of the unsaturated ester (within the range of substrates studied). Furthermore, the small increase in optical purity with increasing steric bulk in the substrate reaches an upper limit as evidenced by comparison of 1-adamantyl and t-butyl. Moreover, in addition to steric factors polar factors appear to play a role in the asymmetric reduction of the free acid (*Z*-α-acetamidocinnamic acid) (81% ee) since the relatively higher stereospecificity observed conflicts with the smaller steric volume of the carboxyl group relative to that of the methyl ester function. Finally, the excess of *R*-configuration in all the reaction products V indicates that with (2*R*, 3*R*)-(—)-DIOP as the chiral ligand in the neutral rhodium—diphosphine complex, preferential attack occurred upon the same *si—re* prochiral

TABLE 1

ASYMMETRIC HYDROGENATION OF *Z*-α-ACETAMIDOCINNAMATE ESTERS, $C_6H_5CH=C(NHCOCH_3)$-COOR, WITH CHLORORHODIUM—(—)-DIOP [a]

R	% conv. [b]	$[\alpha]_D^{25}$	% opt. yield [c]	Abs. config.
H	>97	—38.1 [d]	81.9 [e]	*R* [f]
Me	>97	—70.4 [g]	69.4 [h]	*R* [i]
Et	>97	—61.8 [g]	71.9 [j]	*R*
i-Pr	>97	—57.8 [g]	75.9 [k]	*R*
t-Bu	>97	—57.3 [g]	77.0 [l]	*R*
1-Ada [m]	>97	—72.4 [g]	71.3 [h,n]	*R*

[a] [Rh] = 3.0 mmol l^{-1}; [DIOP]/[Rh] = 1.1; [substrate]/[Rh] = 50; [abs. ethanol]/[benzene] = 2.3; total volume 10 ml; 1 atm. H_2 and 25°C. [b] Determined by NMR and theoretical uptake of H_2. [c] % enantiomeric excess; based upon at least two experiments, two determinations per experiment. [d] Degrees, (*c* 1.0, 95% EtOH), ± 0.6°. [e] Based upon *N*-acetyl-*S*-phenylalanine, $[\alpha]_D^{25}$ +46.5° (*c* 1.0, 95% EtOH), lit. [7] $[\alpha]_D^{25}$ +46.8° (*c* 1.06, 95% EtOH). [f] Lit. [7] 81% ee. [g] Degrees, (*c* 1.0, $CHCl_3$), ±1.0°. [h] Based upon *N*-acetyl-*S*-phenylalanine methyl ester, $[\alpha]_D^{25}$ +101.5° (*c* 1.0, $CHCl_3$). [i] Lit. [3] 55% ee based upon +21.4° value of the methyl ester [13], 74% ee based upon +15.8° value of the methyl ester. [j] Based upon *N*-acetyl-*S*-phenylalanine ethyl ester, $[\alpha]_D^{25}$ +85.9° (*c* 1.0, $CHCl_3$). [k] Based upon *N*-acetyl-*S*-phenylalanine i-propyl ester, $[\alpha]_D^{25}$ +76.1° (*c* 1.0, $CHCl_3$). [l] Based upon *N*-acetyl-*S*-phenylalanine t-butyl ester, $[\alpha]_D^{25}$ +74.4° (*c* 1.0, $CHCl_3$). [m] Due to solubility difficulties of the substrate: [Rh] = 2.0 mmol l^{-1}; total volume 15 ml; other conditions same as in footnote *a*. [n] Methanolysis in abs. methanol saturated with dry HCl gas, 2.5 h at 80°C.

face of the unsaturated ester substrate III irrespective of the size of the alcohol moiety.

The optical purity of the products was determined by comparison with optically-pure standards (see Table 5). In the case of the 1-adamantyl ester, the optical purity was determined by reference to the methyl ester obtained by acid-catalyzed transesterification with absolute methanol.

Using the literature value of $[\alpha]_D^{25}$ +21.4° (*c* 1.9, MeOH) for *N*-acetyl-*S*-phenylalanine methyl ester [13], it was initially found that a large difference in optical purity existed between the saturated methyl ester product (51% ee) and the ethyl ester (72% ee). Much smaller increments in optical purity followed until a maximum of 77% ee was reached with t-butyl, and then a decrease to 53% ee with the 1-adamantyl analogue (based upon the +21.4° methyl ester literature value). When the specific rotation of the saturated methyl ester standard was checked by four independent methods, the literature value was found to be too high (the corrected value being $[\alpha]_D^{25}$ +15.8 ± 0.1° (*c* 2.0, MeOH)). Use of the new methyl ester standard value brought the original 51% ee up to 69% ee (for the methyl ester reaction product), and the 1-adamantyl 53% ee up to 71% ee.

The following methods were used to determine the specific rotation of the saturated methyl ester standard:

S-phenylalanine $[\alpha]_D^{25}$ —33.4° (*c* 2.0, H_2O) (lit. [14] $[\alpha]_D^{25}$ —34.5° and [15] —33.4° both (*c* 2.0, H_2O)) was esterified with methanol/dry HCl according to a modified procedure of Greenstein and Winitz [16], followed by acetylation with acetyl chloride [17] to give *N*-acetyl-*S*-phenylalanine methyl ester, m.p. 86—87°C., $[\alpha]_D^{25}$ + 15.7° (*c* 2.0, MeOH), $[\alpha]_D^{25}$ +101.5° (*c* 1.0, $CHCl_3$).

Next, *N*-acetyl-*S*-phenylalanine $[\alpha]_D^{25}$ +46.5° (*c* 1.0, 95% EtOH) (lit. [7] $[\alpha]_D^{25}$ +46.8° (*c* 1.06, 95% EtOH)) was esterified by diazomethane to give *N*-acetyl-*S*-phenylalanine methyl ester, m.p. 86.0—86.5°C., $[\alpha]_D^{25}$ +15.9° (*c* 2.0,

MeOH), $[\alpha]_D^{25}$ +101.1° (*c* 1.0, $CHCl_3$). The methyl ester produced by this method from *N*-acetyl-*S*-phenylalanine of identical optical rotation was shown by Kagan [7] to give only one peak when analyzed by gas chromatography on a chiral column of *N*-lauroyl-*S*-valine t-butylamide [18] capable of resolving the two enantiomeric methyl esters.

In addition, when *N*-acetyl-*S*-phenylalanine ethyl ester $[\alpha]_D^{20}$ +13.8° (*c* 2.0, 95% EtOH) (lit. [19] $[\alpha]_D^{20}$ —13.1° (*c* 2.6, 95% EtOH) for the *R*-enantiomer) was transesterified with methanol (acid catalyzed) the *N*-acetyl-*S*-phenylalanine methyl ester produced showed $[\alpha]_D^{25}$ +15.9° (*c* 2.0, MeOH).

A fourth check on the accuracy of the methyl standard rotation was performed using transesterification of a diastereomeric mixture of *N*-acetylphenylalanine (—)-menthyl esters [20] whose composition was determined by gas chromatography. Transesterification of this 8.09 : 1.00 (78% ee) mixture with methanol/dry HCl produced *N*-acetylphenylalanine methyl ester $[\alpha]_D^{25}$ +79.1°, $[\alpha]_{434}^{25}$ +180.7° (*c* 1.0, $CHCl_3$). The rotation of the enantiomerically pure *N*-acetyl-*S*-phenylalanine methyl ester was calculated to be $[\alpha]_D^{25}$ +101.4°, and $[\alpha]_{434}^{25}$ +231.7° both at (*c* 1.0, $CHCl_3$).

The rotations of the *N*-acetyl-*S*-phenylalanine methyl ester produced by the four methods are listed in Table 2. On the basis of this evidence, it was decided to use the rotation values of the *N*-acetyl-*S*-phenylalanine methyl ester as listed in Table 5.

The crystalline *N*-acetyl-*S*-phenylalanine t-butyl ester standard compound, m.p. 37—39.5, originally produced was found to be a hemihydrate. When this hemihydrated crystalline material was dried in vacuo over P_2O_5, an oil was obtained whose elemental analysis was in agreement with that of the anhydrous t-butyl ester. Thus, saturated ester reaction products were dried in vacuo prior to determination of their respective rotations.

The exact nature of the active catalytic species in the neutral chlororhodium —DIOP catalyzed hydrogenation reactions has not yet been ascertained [21,22]. Continued systematic studies into the spatial requirements of both substrate and catalyst should provide more insight at the molecular level into these reac-

TABLE 2

ROTATION OF *N*-ACETYL-*S*-PHENYLALANINE METHYL ESTER, $C_6H_5CH_2CH(NHCOCH_3)$-$COOCH_3$, PRODUCED BY VARIOUS METHODS

	Method a [a]	Method b [b]	Method c [c]	Method d [d]
$[\alpha]_D^{25}$ (*c* 2.0, MeOH)	+ 15.7°	+ 15.9°	+15.9°	
$[\alpha]_{434}^{25}$ (*c* 2.0, MeOH)	+ 42.0	+ 42.4		
$[\alpha]_{334}^{25}$ (*c* 2.0, MeOH)	+133.2	+133.8		
$[\alpha]_D^{25}$ (*c* 1.0, $CHCl_3$)	+101.5	+101.1		+101.4
$[\alpha]_{434}^{25}$ (*c* 1.0, $CHCl_3$)	+231.3	+230.5		+231.7
$[\alpha]_{334}^{25}$ (*c* 1.0, $CHCl_3$)	+576.6	+574.9		

[a] Esterification of *S*-phenylalanine followed by acetylation. [b] Esterification of *N*-acetyl-*S*-phenylalanine. [c] Methanolysis of *N*-acetyl-*S*-phenylalanine ethyl ester. [d] Methanolysis of *N*-acetylphenylalanine (—)-menthyl ester 8.09 : 1.00 (78% ee) mixture of diastereomers.

tions. Investigations are currently in progress with analogues of the unsaturated esters III having chiral alcohol moieties, as well as variable temperature studies.

Experimental

The hydrogenations were carried out in a glass apparatus at atmospheric pressure. The hydrogenation vessel (containing a rubber septum) was placed in a thermostatted bath at 25.0 ± 0.5°C. Within the thermostatted bath was placed a submersible magnetic stirrer, and inside the reaction vessel was a Teflon-coated stirring bar.

Absolute methanol was purified by distillation, and absolute ethanol was purified according to Vogel [23]. Benzene was purified as described by Kagan et al. [3]. All solvents were stored under argon, and again deoxygenated with argon before use. Chloro(1,5-cyclooctadiene)rhodium(I) dimer, and (—)-DIOP were purchased from Strem Chemicals Inc. and used as received. *Z*-α-Acetamidocinnamic acid was purchased from Fluka and used as received. *S*-Phenylalanine, *N*-acetyl-*S*-phenylalanine, and *N*-acetyl-*S*-phenylalanine ethyl ester were purchased from Sigma Chemical Co., Inc. and used as received. 1-Adamantanol was purchased from Aldrich Chemical Co., Inc. and used as received.

Melting points are uncorrected. Microanalyses were performed at the Hebrew University of Jerusalem.

The *Z*-4-benzylidene-2-methyl-2-oxazolin-5-one azlactone, m.p. 147—148°C (lit. [9] m.p. 148—150°C) was synthesized according to the method of Herbst and Shemin [9] and dried in vacuo for one week in a desiccator over phosphorus pentoxide.

Z-Methyl-α-acetamidocinnamate

Following the procedure used by Cook et al. [10], a solution of 1.6 g (69 mg-at.) sodium metal in 170 ml absolute methanol was treated with 12.5 g (67 mmol) *Z*-4-benzylidene-2-methyl-2-oxazolin-5-one, and the mixture stirred for 48 h. After neutralization to pH 5 with glacial acetic acid, the mixture was evaporated in vacuo to dryness. The solid residue was dissolved in 400 ml chloroform, and the solution was washed with 300 ml water, dried over anhydrous magnesium sulfate, filtered and again evaporated in vacuo to dryness. The solid residue was dissolved in 250 ml ethyl acetate, refluxed with activated charcoal, filtered, and evaporated in vacuo to dryness. Recrystallization of the residue from ethyl acetate/petroleum ether 60—80° yielded 4.4 g (30% yield) of *Z*-methyl-α-acetamidocinnamate, m.p. 125—127°C. The infrared, NMR, and elemental analysis are listed in Table 3.

Z-Ethyl-α-acetamidocinnamate, *Z*-i-propyl-α-acetamidocinnamate, and *Z*-t-butyl-α-acetamidocinnamate were prepared by similar procedures, and details are given in Table 3. The t-butyl ester was made by use of potassium t-butoxide.

Z-1-Adamantyl-α-acetamidocinnamate

8.0 g (53 mmol) 1-adamantanol was dissolved in 100 ml anhydrous benzene and 3.2 g (70 mg-at.) of 50% sodium dispersion in paraffin was added. After standing 48 h with magnetic stirring, 400 ml anhydrous benzene was added

TABLE 3

CHARACTERIZATION OF *Z*-α-ACETAMIDOCINNAMATE ESTERS, $C_6H_5CH{=}C(NHCOCH_3)COOR$

R	M.p. [a]	Infrared [b]	NMR [c]		Mol. formula	Analysis found (calcd.)		
						C	H	N
Me	125—127	3130 (N—S s) [d]	7.33 ± 0.15 (m)	6H-PhH, PhCH	$C_{12}H_{13}NO_3$	65.91	6.02	6.73
		1725 (C=O s, ester)	6.93 (broad s)	1H-NH		(65.75)	(5.94)	(6.39)
		1655 (C=O s, amide)	3.78 (s)	3H-CH_3O				
		1525 (N—H b) [e]	2.03 (s)	3H-CH_3C=O				
Et	91— 92	3235 (N—H s)	7.35 ± 0.35 (m)	7H-PhH, PhCH, NH	$C_{13}H_{15}NO_3$	67.01	6.68	5.94
		1710 (C=O s, ester)	4.21 (q)	2H-OCH_2, *J* 7.5 Hz		(66.95)	(6.44)	(6.01)
		1660 (C=O s, amide)	2.03 (s)	3H-CH_3C=O				
		1515 (N—H b)	1.32 (t)	3H-CH_3, *J* 7.5 Hz				
i-Pr	121—123	3200 (N—H s)	7.31 ± 0.15 (m)	6H-PhH, PhCH	$C_{14}H_{17}NO_3$	68.12	7.18	5.55
		1705 (C=O s, ester)	7.07 (broad s)	1H-NH		(68.02)	(6.88)	(5.67)
		1655 (C=O s, amide)	5.05 (septet)	1H-OCH, *J* 6 Hz				
		1515 (N—H b)	2.01 (s)	3H-CH_3C=O				
			1.30 (d)	6H-CH_3, *J* 6 Hz				
t-Bu	149—151	3220 (N—H s)	7.30 ± 0.15 (m)	7H-PhH, PhCH, NH	$C_{15}H_{19}NO_3$	69.02	7.19	5.76
		1705 (C=O s, ester)	2.01 (s)	3H-CH_3C=O		(68.97)	(7.28)	(5.36)
		1660 (C=O s, amide)	1.51 (s)	9H-CH_3				
		1520 (N—H b)						
1-Ada	183—184	3260 (N—H s)	7.31 ± 0.15 (m)	6H-PhH, PhCH	$C_{21}H_{25}NO_3$	74.55	7.57	4.14
		1715 (C=O s, ester)	6.82 (broad s)	1H-NH		(74.34)	(7.38)	(4.13)
		1655 (C=O s, amide)	2.18 (broad s)	9H-AdH				
		1495 (N—H b)	2.02 (s)	3H-CH_3C=O				
			1.67 (broad s)	6H-AdH				

[a] Degrees, centrigrade. [b] cm^{-1}, KBr pellet. [c] δ, $CDCl_3$/TMS, 100 MHz, m = multiplet, s = singlet, d = doublet, t = triplet, q = quadruplet. [d] s = stretching. [e] b = bending.

followed by 4.4 g (24 mmol) of *Z*-4-benzylidene-2-methyl-2-oxazolin-5-one. The mixture was refluxed for 6 h. Work-up similar to that for the corresponding methyl ester gave, after column chromatography on a silica-gel column (eluted with an increasing gradient of ethyl acetate in petroleum ether 40—60°), 3.9 g (48% yield) of *Z*-1-adamantyl-α-acetamidocinnamate, m.p. 183—184°C. The infrared, NMR, and elemental analysis are listed in Table 3.

N-Acetyl-S-phenylalanine methyl ester

Method a: 1.1 g (6.7 mmol) *S*-phenylalanine $[\alpha]_D^{25}$ —33,4° (*c* 2.0, H_2O) {lit. [14] $[\alpha]_D^{25}$ —34.5° and [15] —33.4° both (*c* 2.0, H_2O)} was placed in a pressure bottle containing absolute methanol saturated with dry HCl gas, and the mixture heated for 4 h at 75°C. Evaporation in vacuo to dryness at 35°C followed by storage for 24 h in vacuo in a desiccator over KOH pellets, and recrystallization from methanol/ether gave 1.2 g (84% yield) of needle-like crystals of *S*-phenylalanine methyl ester hydrochloride, m.p. 153—154°C (lit. [24] m.p. 159—161°C). The infrared and NMR spectra are listed in Table 4.

1.18 g (5.5 mmol) *S*-phenylalanine methyl ester hydrochloride was added to 60 ml anhydrous benzene and 0.76 ml (5.5 mmol) triethylamine (see ref. [17]). After cooling to 0°C, an additional 0.76 ml (5.5 mmol) triethylamine was added, followed by 0.43 ml (6.0 mmol) acetyl chloride. The reaction mixture was brought to room temperature, and stirred magnetically for 1 h. After filtering off of the triethylamine hydrochloride precipitate, the filtrate was evaporated in vacuo to dryness at 35°C. Column chromatography on a silica-gel column (prepared in petroleum ether 40—60° and eluted with an increasing gradient of ethyl acetate in petroleum ether 40—60°) gave an oil which solidified. Recrystallization from ethyl acetate/petroleum ether 60—80° gave *N*-acetyl-*S*-phenylalanine methyl ester, m.p. 86—87°C, $[\alpha]_D^{25}$ +15.7° (*c* 2.0, MeOH) and $[\alpha]_D^{25}$ +101.5° (*c* 1.0, $CHCl_3$). Lit. [13] $[\alpha]_D^{25}$ +21.4° (*c* 1.9, MeOH) and [25] $[\alpha]_D^{25}$ +17.8 ± 1.2° (*c* 2, MeOH) m.p. 90°C. The infrared and NMR spectra are listed in Table 5.

Method b: 0.5 g *N*-acetyl-*S*-phenylalanine $[\alpha]_D^{25}$ +46.5° (*c* 1.0, 95% EtOH) (lit. [7] $[\alpha]_D^{25}$ +46.8° (*c* 1.06, 95% EtOH)) was added to 30 ml diethyl ether, and treated with an ethereal solution of diazomethane. After the starting material had dissolved, the solution was allowed to stand for 0.5 h. Evaporation in vacuo to dryness followed by column chromatography and recrystallization as described under (a) gave *N*-acetyl-*S*-phenylalanine methyl ester, m.p. 86.0—86.5°C, $[\alpha]_D^{25}$ +15.9° (*c* 2.0, MeOH) and $[\alpha]_D^{25}$ +101.1° (*c* 1.0, $CHCl_3$). The TLC R_f value, infrared, and NMR spectra were identical with those found in method a. The specific rotations at different wavelengths and in various solvents are listed in Table 2.

Method c: 0.5 g *N*-acetyl-*S*-phenylalanine ethyl ester $[\alpha]_D^{20}$ +13.8° (*c* 2.0, 95% EtOH) (lit. [19] $[\alpha]_D^{20}$ —13.1° (*c* 2.6, 95% EtOH) for *R*-isomer) was refluxed in 50 ml absolute methanol containing 50 mg *para*-toluenesulfonic acid for 4 days. Upon cooling, the reaction mixture was evaporated in vacuo to dryness, and then chromatographed on a silica gel column as described in method a to give *N*-acetyl-*S*-phenylalanine methyl ester, $[\alpha]_D^{25}$ +15.9° (*c* 2.0, MeOH). The TLC R_f value, infrared, and NMR spectra were identical with those found in methods a and b.

TABLE 4

CHARACTERIZATION OF *S*-PHENYLALANINE ESTER HYDROCHLORIDES, $C_6H_5CH_2CH(NH_2)COOR \cdot HCl$

R	M.p. [a]	$[\alpha]_D^{25}$ [b]	Infrared [c]	NMR [d]			Mol. formula	Analysis found (calcd.)		
								C	H	N
Me	153–154 [e]	+34.8 [f,g]	2905 (N–H s) [h]	8.79 (broad s)	2H-NH_2					
			1745 (C=O s)	7.20 (s)	5H-PhH					
			1580 (N–H b) [i]	4.14 (d of d)	1H-NCH,	*J* 7.5 Hz				
			1495 (N–H b)			*J* 5.5 Hz				
				3.60 (s)	3H-OCH_3					
				3.21 (lower *AB* quartet)	1H-CH_2C*,	*J* 13.5 Hz				
						J 5.5 Hz				
				3.11 (upper *AB* quartet)	1H-CH_2C*,	*J* 13.5 Hz				
						J 7.5 Hz				
i-Pr	202–204	+37.2 [f]	2960 (N–H s)	8.86 (broad s)	2H-NH_2		$C_{12}H_{18}NO_2Cl$	59.33	7.42	5.87
			1740 (C=O s)	7.21 (s)	5H-PhH			(59.14)	(7.39)	(5.75)
			1585 (N–H b)	4.80 (septet)	1H-OCH,	*J* 6 Hz				
			1500 (N–H b)	4.06 (d of d)	1H-NCH,	*J* 9 Hz				
						J 5 Hz				
				3.30 (lower *AB* quartet)	1H-CH_2C*	*J* 14 Hz				
						J 5 Hz				
				3.05 (upper *AB* quartet)	1H-CH_2C*	*J* 14 Hz				
						J 9 Hz				
				1.07 (d of d)	6H-CH_3)$_2$C	*J* 13 Hz				
						J 6 Hz				
t-Bu	207–208 (dec.) [j]	+45.2 [k]	2925 (N–H s)	8.75 (broad s)	2H-NH_2					
			1730 (C=O s)	7.20 (s)	5H-PhH					
			1575 (N–H b)	3.99 (d of d)	1H-NCH,	*J* 9 Hz				
			1495 (N–H b)			*J* 5 Hz				
				3.26 (lower *AB* quartet)	1H-CH_2C*,	*J* 14 Hz				
						J 5 Hz				
				2.99 (upper *AB* quartet)	1H-CH_2C*,	*J* 14 Hz				
						J 9 Hz				
				1.29 (s)	9H-CH_3					

[a] Degrees, centrigrade. [b] Degrees. [c] cm^{-1}, KBr pellet. [d] δ, DMSO-d_6/TMS, 100 MHz, s = singlet, d = doublet. [e] Lit. [24] m.p. 159–161°C. [f] (c 1.0, abs. EtOH). [g] Lit. [24] $[\alpha]_D^{25}$ −4.6° (c 5.0, H_2O) not determined under these conditions due to insufficient amount of sample. [h] s = stretching. [i] b = bending. [j] Lit. [26] m.p. (dec.). [k] (c 2.0, abs. EtOH), lit. [26] $[\alpha]_D^{25}$ +44.2° (c 2, EtOH).

Method d: 0.5 g *N*-acetylphenylalanine (—)-menthyl ester (78% epimeric excess) (analyzed by gas chromatography to contain the two diastereomers in a ratio of 8.09 : 1.00) [20] was transesterified in a pressure tube containing 50 ml absolute methanol saturated with dry HCl gas and heated for 2 h at 75° C. After purification as in method a, the *N*-acetylphenylalanine methyl ester gave $[\alpha]_D^{25}$ +79.1°, $[\alpha]_{434}^{25}$ +180.7° both (*c* 1.0, $CHCl_3$). The rotation of the enantiomerically pure *N*-acetyl-*S*-phenylalanine methyl ester was calculated to be $[\alpha]_D^{25}$ +101.4°, $[\alpha]_{434}^{25}$ +231.7° both (*c* 1.0, $CHCl_3$). The TLC R_f value, infrared, and NMR spectra were identical with those found in methods a—c.

N-Acetyl-*S*-phenylalanine i-propyl ester was prepared by a procedure similar to that described in method a. The characterization of the intermediate *S*-phenylalanine i-propyl ester hydrochloride is in Table 4, while that of the *N*-acetyl-*S*-phenylalanine i-propyl ester product is given in Table 5.

N-Acetyl-S-phenylalanine t-butyl ester

S-Phenylalanine t-butyl ester hydrochloride was prepared as described by Roeske [26] and is characterized in Table 4. The acetylation was then performed as described for the corresponding methyl ester (method a). The reaction product was purified via column chromatography as described in method a to give an oil. After repeated unsuccessful attempts at crystallization, the oil was triturated in petroleum ether 40—60° at liquid nitrogen temperature. After repeated attempts a solid formed which was recrystallized from petroleum ether 60—80° to give *N*-acetyl-*S*-phenylalanine t-butyl ester hemihydrate, m.p. 37—39.5° C, $[\alpha]_D^{25}$ +72.3° (*c* 1.0, $CHCl_3$). Anal.: Found: C, 66.39; H, 7.78; N, 5.42. $C_{15}H_{21}NO_3 \cdot \frac{1}{2}H_2O$ calcd.: C, 66.15; H, 8.14; N, 5.14%.

The crystalline hemihydrate solid was dried 7 days in vacuo in a desiccator over phosphorus pentoxide to give anhydrous *N*-acetyl-*S*-phenylalanine t-butyl ester as an oil. No attempt was made to crystallize this oil. The rotation, infrared, NMR, and elemental analysis are given in Table 5.

Hydrogenation

The chlororhodium—DIOP complex was prepared in a 10 ml round bottom flask under argon from 7.4 mg (1.5×10^{-2} mmol) chloro(1,5-cyclooctadiene)-rhodium(I) dimer and 16.5 mg (3.3×10^{-2} mmol) (—)-DIOP in 3 ml benzene with magnetic stirring. The solution was transferred by syringe and injected through a septum into an empty 25 ml hydrogenation vessel (with stirrer) connected to the atmospheric-pressure hydrogenation apparatus (preflushed with hydrogen). Prehydrogenation for 10 min was followed by injection through the septum via syringe of 1.5 mmol of the *Z*-α-acetamidocinnamate ester in 7 ml absolute ethanol. Due to solubility difficulties, *Z*-1-adamantyl-α-acetamidocinnamate was dissolved in 10.5 ml absolute ethanol, and the chlororhodium—DIOP complex was prepared in 4.5 ml of benzene, keeping the solvent ratio the same as with the other esters.

Work-up of the hydrogenation product

The homogeneous solutions were evaporated in vacuo to dryness, and a quantity removed for NMR analysis in a Varian XL-100 to determine the percent conversion. The remainder of the solid residue was taken up in the minimum

(continued on p. 260)

TABLE 5

CHARACTERIZATION OF *N*-ACETYLPHENYLALANINE ESTERS, $C_6H_5CH_2CH(NHCOCH_3)COOR$

R	M.p. [a]	$[\alpha]_D^{25}$ [b]	Abs. config.	Infrared [c]	NMR [d]			Mol. formula	Analysis found (calcd.)		
									C	H	N
Me	86.0–86.5 [e]	+101.3 [f]	*S*	3310 (N–H s) [l]	7.06 ± 0.15 (m)	5H-Ph<u>H</u>					
		+230.9 [g]		1745 (C=O s, ester)	6.01 (broad d)	1H-N<u>H</u>,	*J* 8 Hz				
		+575.8 [h]		1660 (C=O s, amide)	4.80 (d of t)	1H-C<u>H</u>,	*J* 8 Hz				
				1520 (N–H b) [j]			*J* 6 Hz				
					3.65 (s)	3H-OC<u>H</u>$_3$					
					3.06 (d)	2H-C<u>H</u>$_2$Ph,	*J* 6 Hz				
					1.93 (s)	3H-C<u>H</u>$_3$C=O					
Et	85 –86	+ 85.9 [f]	*S*	3290 (N–H s)	7.16 ± 0.25 (m)	5H-Ph<u>H</u>					
		+198.5 [g]		1730 (C=O s, ester)	5.94 (broad d)	1H-N<u>H</u>,	*J* 8 Hz				
		+502.8 [h]		1640 (C=O s, amide)	4.78 (d of t)	1H-C<u>H</u>,	*J* 8 Hz				
				1530 (N–H b)			*J* 6 Hz				
					4.10 (q)	2H-OC<u>H</u>$_2$,	*J* 7.5 Hz				
					3.06 (d)	2H-C<u>H</u>$_2$Ph,	*J* 6 Hz				
					1.95 (s)	3H-C<u>H</u>$_3$C=O					
					1.22 (t)	3H-C<u>H</u>$_3$,	*J* 7.5 Hz				
i-Pr	71.0–71.5	+ 76.1 [f]	*S*	3280 (N–H s)	7.09 ± 0.15 (m)	5H-Ph<u>H</u>		$C_{14}H_{19}NO_3$	67.73	7.89	5.59
		+175.0 [g]		1725 (C=O s, ester)	6.17 (broad d)	1H-N<u>H</u>,	*J* 7 Hz		(67.47)	(7.63)	(5.62)
		+447.4 [h]		1655 (C=O s, amide)	4.86 ± 0.24 (m)	2H-OC<u>H</u>, NC<u>H</u>					
				1535 (N–H b)	3.04 (d)	2H-C<u>H</u>$_2$Ph,	*J* 6.5 Hz				
					1.93 (s)	3H-C<u>H</u>$_3$C=O					
					1.18 (d of d)	6H-C<u>H</u>$_3$)$_2$C,	*J* 6 Hz, *J* 4 Hz				

t-Bu	*k*	+ 74.4 *f,l*	*S*	3215 (N—H s)	7.09 ± 0.13 (m)	5H-PhH		$C_{15}H_{21}NO_3$	68.44	7.99	5.32
		+170.2 *g*		1720 (C=O s, ester)	6.00 (broad d)	1H-NH,	*J* 8 Hz		(68.35)	(8.08)	(5.56)
		+431.6 *h*		1655 (C=O s, amide)	4.69 (d of t)	1H-CH,	*J* 8 Hz				
				1525 (N—H b)			*J* 6 Hz				
					3.03 (d)	$2H\text{-}CH_2Ph$,	*J* 6 Hz				
					1.94 (s)	$3H\text{-}CH_3C{=}O$					
					1.40 (s)	$9H\text{-}CH_3$					
1-Ada	*m*	+ 37.4 *f,n*	*S*	3245 (N—H s)	7.18 ± 0.22 (m)	5H-PhH					
		+ 91.2 *g,n*		1730 (C=O s, ester)	5.96 (broad d)	1H-NH,	*J* 8 Hz				
				1650 (C=O s, amide)	4.68 (d of t)	1H-CH,	*J* 8 Hz				
				1540 (N—H b)			*J* 6 Hz				
					3.03 (d)	$2H\text{-}CH_2Ph$,	*J* 6 Hz				
					2.04 (m)	9H-AdH					
					1.93 (s)	$3H\text{-}CH_3C{=}O$					
					1.62 (m)	6H-AdH					

[a] Degrees, centrigrade. [b] Degrees (*c* 1.0, $CHCl_3$). [c] cm^{-1}, KBr pellet. [d] δ, $CDCl_3$/TMS, 100 MHz, s = singlet, d = doublet, t = triplet, m = multiplet. [e] Lit. [25] m.p. 90°C. [f] Sodium-D (589 nm). [g] 434.75 nm. [h] 334.15 nm. [i] s = stretching. [j] b = bending. [k] Oil, hemihydrate m.p. 37.0—39.5°C. [l] Hemihydrate $[\alpha]_D^{25}$ +72.3° (*c* 1.0, $CHCl_3$). [m] Data given for hydrogenation reaction product only, material was a viscous oil. [n] Estimated minimum rotation based upon $[\alpha]_D^{25}$ −26.7°, $[\alpha]_{434}^{25}$ −65.0° (*c* 1, $CHCl_3$) yielding 71.3% ee *R*-methyl ester by acid-catalyzed transesterification.

quantity of chloroform and chromatographed on a silica gel column (prepared in petroleum ether 40—60°), elution with an increasing gradient of ethyl acetate in petroleum ether 40—60°. The purified *N*-acetylphenylalanine ester products were stored in a desiccator in vacuo over phosphorus pentoxide prior to determination of the rotation in a Perkin—Elmer MC-141 polarimeter. The rotation was measured at three wavelengths: 589 (sodium-D), 434.75, and 334.15 nm; 25°C and a concentration of 1.0×10^{-2} g ml^{-1} in chloroform.

Methanolysis of N-acetylphenylalanine 1-adamantyl ester hydrogenation reaction product

0.5 g *N*-acetylphenylalanine 1-adamantyl ester $[\alpha]_D^{25}$ −26.7° (*c* 1.0, $CHCl_3$) was transesterified with methanol/dry HCl for 2.5 h similar to the procedure described in method d for the corresponding methyl ester. After purification as in method a, the *N*-acetylphenylalanine methyl ester gave $[\alpha]_D^{25}$ −72.4° (*c* 1.0, $CHCl_3$) for 71.3% ee of the *R*-enantiomer. The TLC R_f value, infrared, and NMR were identical with those of an authentic sample of the methyl ester.

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