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

## STERIC AND ELECTRONIC FACTORS IN THE ASYMMETRIC HOMOGENEOUS HYDROGENATION OF Z-α-ACYLAMINOCINNAMIC ACIDS AND ESTERS CATALYZED BY RHODIUM(I) COMPLEXES OF DIOP

ROBERT GLASER* and SHIMONA GERESH
Department of Chemistry, Ben Gurion University of the Negev, Beersheva, Israel

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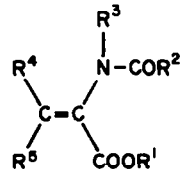
**Abstract**—Z-α-acylaminocinnamic acids and esters were hydrogenated with rhodium(I) complexes containing (4R,5R) - *trans* - 4,5 - bis(diphenylphosphinomethyl) - 2,2 - dimethyl - 1,3 - dioxolan (DIOP). Increasing the steric bulk of the acyl function (NHCOR, where R is an alkyl moiety) resulted in a lowered reduction of the si-re prochiral face to yield a decreasing excess of the (R)-amino acid derivatives. In the series of N-acylphenylalanine free acids (resulting from hydrogenation of Z-α-acylaminocinnamic acids) the optical purity decreased from 82% ee-(R) [Me]; 57% ee-(R) [i-Pr]; 52% ee-(R) [t-Bu]; to 46% ee-(R) [1-adamantyl]. The α-benzamido, α-formamido and α-trifluoroacetamido substrates gave hydrogenation products having 68% ee-(R) [Ph]; 60% ee-(R) [H]; and 16% ee-(R) [$CF_3$]. In the corresponding methyl esters, increasing the steric bulk of the acyl function (NHCOR) resulted in a markedly greater decrease in enantioface differentiation. In the series of N-acylphenylalanine methyl ester products (resulting from hydrogenation of Z-methyl α-acylaminocinnamates) the optical purity decreased from 69% ee-(R) [Me]; 15% ee-(R) [i-Pr]; to 0% ee [t-Bu and 1-adamantyl]. The α-benzamido, α-formamido, and α-trifluoroacetamido substrates gave hydrogenation products having 36% ee-(R) [Ph]; 58% ee-(R) [H]; and 22% ee-(S) [$CF_3$].

In the series of N-acetylphenylalanine alkyl ester products (resulting from hydrogenation of Z-alkyl α-acetamidocinnamate esters) trifluoro substitution in the alkyl alcohol moiety resulted in a decrease in optical purity to 52% ee-(R) [$CH_2CF_3$] compared to 72, 76 and 77% ee-(R) [Et, i-Pr and t-Bu, respectively].

We have been engaged over the last few years in investigating the structural requisites in chiral diphosphine-rhodium(I) hydrogenation complexes. As structural probes we have utilized N-acyldehydroamino acid derivatives (1) in which the steric and/or electronic nature of the substituents $R^1$ to $R^5$ can be systematically varied. These prochiral olefins give reduction products (formed via use of the above-mentioned catalysts) which generally show quite high optical purities. The high degree of enantioface selectivity can be rationalized as arising from intimate and specific interactions between the chiral diphosphine/rhodium(I) hydrogenation complex and the prochiral dehydroamino acid derivative, 1.



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This present work will report upon the steric and electronic nature of the $R^1$ and $R^2$ moieties and their effect upon the optical purity of the reduction products of olefin 1. Some of these findings have been previously communicated in preliminary form.[2,3]

### RESULTS AND DISCUSSION

Z-α-acylaminocinnamic acids and esters were prepared via ring opening of the corresponding Z-4-benzylidene-2-alkyl or aryl-2-oxazolin-5-one azlactones. The assignment of Z-configuration to these olefins has been made using $^1H$ NMR spectroscopy[4,5] and is ultimately based upon the X-ray structure determination of Z-α-benzamidocinnamic acid.[6] The $^1H$ NMR spectra (100 MHz, $CDCl_3$/TMS) of the parent Z-4-benzylidene-2-alkyl-2-oxazolin-5-ones (alkyl = methyl, i-propyl, t-butyl, and 1-adamantyl) all show the $H_\beta$-vinylic proton signal at $7.02 \pm 0.1\ \delta$ (singlet). The Z-configuration of the trifluoroacetamido substrates were proven by Breitholle and Stammer.[7]

The Z-α-acylaminocinnamic acids and esters (in EtOH/benzene 2.3:1.0 solvent mixture) underwent reduction catalyzed by homogeneous rhodium(I) complexes [prepared *in-situ* from (4R,5R) - *trans* - 4,5 - bis(diphenylphosphinomethyl) - 2,2 - dimethyl - 1,3 - dioxolan (DIOP), 2, and chloro(1,5 - cyclooctadiene)rhodium(I) dimer, 3] (see Scheme, in which $R^3 = R^5 = H$ and $R^4 = Ph$). The optical purities of the resulting N-acylphenylalanine free acid and ester reduction products, 4, are listed in Tables 1 and 2.

In the past, we have shown that *in situ* prepared DIOP/Rh(I) hydrogenation complexes are not particularly sensitive to the steric bulk of the alcohol moiety $R^1$ in Z-alkyl α-acetamidocinnamate esters, $C_6H_5CH = C(NHCOCH_3)COOR^1$: 69% enantiomeric excess-(R) [$R^1$=Me]; 72% ee-(R) [Et]; 76% ee-(R) [i-Pr]; and 77% ee-(R) [t-Bu].[3] The corresponding free acid shows an optical purity of 82% ee-(R) [H] whose magnitude is not commensurate with the steric size of the carboxylic acid moiety alone.[3] In Table 1 it is shown that changing the polar/electronic nature of the $R^1$ group from $CH_2CH_3$ to

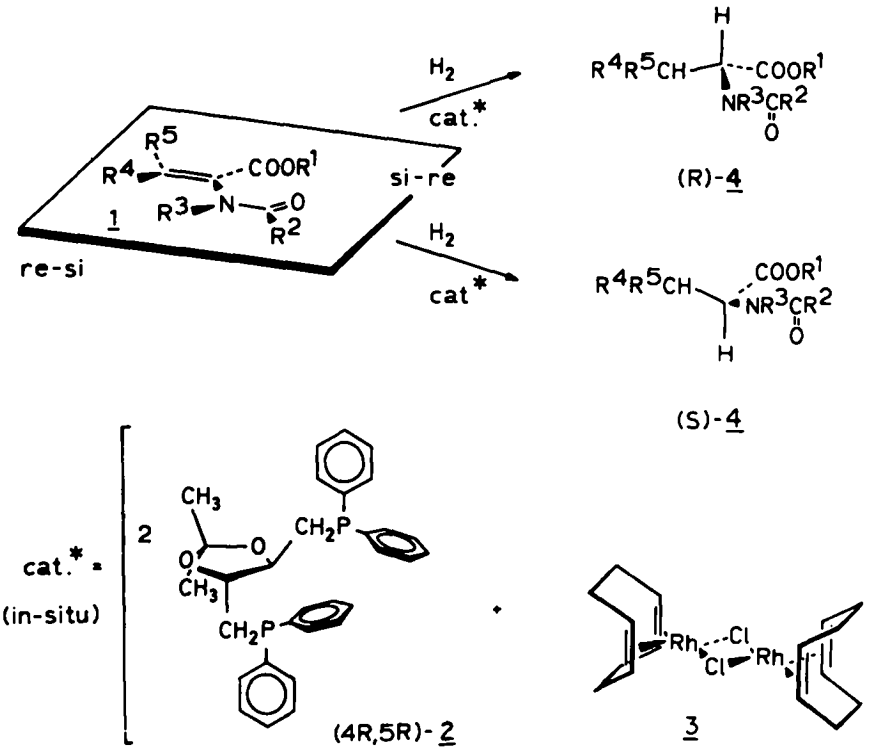


Table 1. Asymmetric hydrogenation of Z-α-acylaminocinnamic acids, $C_6H_5CH = C(NHCOR^2)COOH$, catalyzed by *in situ* Rh(I)/(4R,5R)-DIOP[a]

| $R^2$ | % conversion[b] | $[\alpha]_D^{25}$[c] | % opt. purity[d] | abs. config. |
|---|---|---|---|---|
| H | 40 | - | 60[e,f] | R |
| Me | ∿100 | -84.3 | 83[g] | R |
| i-Pr | ∿100 | -51.7 | 57[h] | R |
| t-Bu | ∿100 | -37.9 | 52[i] | R |
| 1-Ada | ∿100 | -29.5 | 46[j] | R |
| Ph | ∿100 | +30.6 | 68[k] | R |
| $CF_3$ | 58 | - | 16[l] | R |

[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. All free acid reduction products converted to methyl esters via diazomethane prior to determination of optical purity. [b]Determined by $^1H$ NMR (acid and ester products) and gas chromatography (ester products); all reactions terminated after 24 hr. [c]$10^{-1} \times [\alpha]$ = degree $g^{-1}$ $cm^2$; (C 1.0, $CHCl_3$) with the exception of N-benzoylphenylalanine methyl ester (C 1.0, 95% EtOH). [d]% enantiomeric excess; ±1% (with the exception of product from Z-α-formamidocinnamic acid, ±5%). [e]Optical rotation corrected for presence of olefin found in sample of methyl ester [g.l.p.c. analysis after purification via silica gel chromatography]. [f]Based upon N-formyl-(S)-phenylalanine methyl ester: $[\alpha]_D^{25}$ + 99.0° (C 1.0, $CHCl_3$). [g]Based upon N - acetyl - (S) - phenylalanine methyl ester: $[\alpha]_D^{25}$ + 101.3° (C 1.0, $CHCl_3$), Ref. 3. [h]Based upon N - isobutyryl - (S) - phenylalanine methyl ester: $[\alpha]_D^{25}$ + 90.8° (C 1.0, $CHCl_3$). [i]Based upon N - pivalyl - (S) - phenylalanine methyl ester: $[\alpha]_D^{25}$ + 73.5° (C 1.0, $CHCl_3$). [j]Based upon N - adamantyl - 1 - carbonyl - (S) - phenylalanine methyl ester: $[\alpha]_D^{25}$ + 63.7° (C 1.0, $CHCl_3$). [k]Based upon N - benzoyl - (S) - phenylalanine methyl ester: $[\alpha]_D^{25}$ − 45.3° (C 1.3, 95% EtOH), Ref. 8. % ee lit.[g] 70% ee-(R) [acid] and 37.5% ee-(R) [ester]. [l]Based upon gas chromatographic separation of (R) & (S)-enantiomers of methyl ester using column containing N-lauroyl-(S)-valine 2 - methyl - 2 - heptadecylamide; % ee based upon difference of peak areas. [m]Based upon N - trifluoroacetyl - (S) - phenylalanine methyl ester: $[\alpha]_D^{25}$ + 100.0° (C 1.0, $CHCl_3$). [n]Value of the methyl ester obtained via acid catalyzed transesterification. [o]Based upon N - acetyl - (S) - phenylalanine ethyl ester: $[\alpha]_D^{25}$ + 85.9° (C 1.0, $CHCl_3$), Ref. 3. [p]Based upon N-acetyl-(S)-phenylalanine i-propyl ester: $[\alpha]_D^{25}$ + 76.1° (C 1.0, $CHCl_3$), Ref. 3. [q]Based upon N-acetyl-(S)-phenylalanine t-butyl ester: $[\alpha]_D^{25}$ + 74.4° (C 1.0, $CHCl_3$), Ref. 3.

Table 2. Asymmetric hydrogenation of Z-alkyl α-acylaminocinnamate esters, $C_6H_5CH=C(NHCOR^2)COOR^1$, catalyzed by *in situ* Rh(I)/(4R,5R)-DIOP[a]

| $R^1$ | $R^2$ | % conversion[b] | $[\alpha]_D^{25}$[c] | % opt. purity[d] | abs. config. |
|---|---|---|---|---|---|
| Me | H | ∿100 | -57.8 | 58[f] | R |
| Me | Me | ∿100 | -70.4 | 69[g] | R |
| Me | i-Pr | ∿100 | -13.8 | 15[h] | R |
| Me | t-Bu | ∿100 | 0 | 0 | R |
| Me | 1-Ada | ∿100 | 0 | 0 | R |
| Me | Ph | ∿100 | +16.0 | 35[k] | R |
| Me | $CF_3$ | 89 | +21.6 | 22[m] | S |
| $CH_2CF_3$ | Me | ∿100 | -52.9[n] | 52[g] | R |
| Et | Me | ∿100 | -61.8 | 72[o] | R |
| i-Pr | Me | ∿100 | -57.8 | 76[p] | R |
| t-Bu | Me | ∿100 | -57.3 | 77[q] | R |

(See Table 1.)

$CH_2CF_3$ resulted in a decrease in the degree of hydrogenation of the si-re prochiral face: 52% ee-(R) [$CH_2CF_3$] vs 72% ee-(R) [$CH_2CH_3$]. The interpretation of the $CH_2CF_3$ result mainly in terms of polar/electronic effects is justifiable since we have seen that the $R^1$ moiety exhibits an insignificant steric bulk effect.

In Table 2, it can be seen that increasing the steric bulk of the acylamino function ($NHCOR^2$, where $R^2$ is an alkyl moiety) resulted in less reduction of the si-re prochiral face to yield a decreasing excess of the (R)-amino acid derivatives. In the series of N-acylphenylalanine free acids [resulting from hydrogenation of Z-α-acylaminocinnamic acids, $C_6H_5CH=C(NHCOR^2)COOH$] the optical purity decreased from 82% ee-(R) [$R^2$ = Me]; 57% ee-(R) [i-Pr]; 52% ee-(R) [t-Bu]; to 46% ee-(R) [1-adamantyl]. The α-benzamido, α-formamido and α-trifluoroacetamido substrates gave hydrogenation products having 68% ee-(R) [Ph]; 60% ee-(R) [H]; and 16% ee-(R) [$CF_3$]. In the corresponding methyl esters, increasing the $R^2$ steric bulk in the acylamino function resulted in a considerably sharper decrease in enantioface differentiation. In the series of N-acylphenylalanine methyl ester products [resulting from hydrogenation of Z-methyl α-acylaminocinnamates, $C_6H_5CH=C(NHCOR^2)COOCH_3$] the optical purity decreased from 69% ee-(R) [$R^2$ = Me]; 15% ee-(R) [i-Pr]; to 0% ee [t-Bu and 1-adamantyl]. The α-benzamido, α-formamido and α-trifluoroacetamido substrates gave hydrogenation products having 36% ee-(R) [Ph]; 58% ee-(R) [H]; and 22% ee-(S) [$CF_3$].

A comparison of the above results for the free acid and methyl ester substrates shows that the free carboxylic acid function appears to restrain the steric bulk effect of the $R^2$ moiety. In both the case of the free acid and of the methyl ester, the benzamido substrates [$R^2$ = Ph] gave reduction product optical purities intermediate between those of the acetamido and isobutyramido substrates. Kagan *et al.*[8] investigated Z-α-benzamidocinnamic acids and methyl esters having electron withdrawing or electron releasing *para*-substituents on the benzamido moiety. Their results with DIOP/Rh(I) complexes do not indicate the presence of a simple correlation between the Hammett sigma values of the *para*-substituent and the optical purity of the product. However, insight into the polar/electronic nature of the $R^2$ moiety is gained when one considers the results for the trifluoroacetamido substrates. In both the case of the free acid and of the methyl ester there is a markedly lower reduction of the si-re prochiral face than is commensurate with the steric size of the trifluoromethyl group alone. The trifluoromethyl group has been described by Pirkle *et al.*[9] as having a van der Walls diameter (5.1 Å) that is intermediate between those of the Me and t-Bu groups. Thus, we can ascribe the observed behaviour of the trifluoroacetamido olefins to the known electron withdrawing character of the $CF_3$-group.

The formamido substrates also exhibit behavior that is not commensurate with the steric size of the aldehydic proton alone. By $^1H$ NMR spectroscopy, it has been shown that Z-methyl β-alkyl or aryl-α-formamidoacrylates, $R^4CH=C(NHCOH)COOCH_3$) exist in $CDCl_3$/TMS in both *trans*- and *cis*-amide conformations, while in this solvent the other alkylacylamino analogues ($R^2 \geq$ Me) only exhibit signals corresponding to the *trans*-amide conformer.[5] Preliminary asymmetric hydrogenation results of the formamidoacrylate olefins do not show a simple correlation between product optical purity and the extent of *trans*/*cis*-amide equilibria in the olefin.

An alternative interpretation is that the NCO moiety prefers a small electron donating alkyl group (i.e. Me) to be adjacent to it. It is reasonable to expect that an adjacent Me group can more effectively satisfy the requirements of a partially positively charged carbonyl C-atom than can an aldehydic proton. The results observed with the trifluoroacetamido olefins are consistent with the latter interpretation.

It was found that the rates of hydrogenation of Z-methyl α-acylaminocinnamates decreased in the following order: isobutyramido, benzamido, pivalamido, adamantyl-1-carboxamido, formamido and trifluoroacetamido. The rates of hydrogenation of the corresponding free acids were comparable to their

methyl ester analogues with the exception of the formamido and trifluoroacetamido analogues which were exceptionally slow.

In the previous article in this series we have shown that N-methylation of the acetamido moiety in Z-α-N-methylacetamidocinnamic acid and its methyl ester did not result in a marked change in the enantioface differentiation by the *in situ* Rh(I)/DIOP catalyst.[1] Z-α-N-methylacetamidocinnamic acid gave a reduction product showing 87% ee(R) [$R^3$ = Me] vs 82% ee-(R) [$R^3$ = H], while the methyl ester showed 73% ee-(R) [$R^3$ = Me] vs 69% ee-(R) [$R^3$ = H].[1]

In conclusion, the systematic studies described in this paper were undertaken to provide information on the steric and polar/electronic requirements of the carboxyl and acylamino moieties in N-acyldehydroamino acid derivatives used in asymmetric hydrogenation. Using *in situ* Rh(I)/DIOP complexes it was found that the carboxyl moiety showed a sensitivity to polar/electronic effects and a relative insensitivity to steric factors. On the other hand, in the acylamino moiety both types of factors appear to play a primary role in the enantioface differentiation process.

## EXPERIMENTAL

Hydrogenations were carried out in a glass atmospheric pressure apparatus at 25 ± 0.5° according to the method described in Refs. 3, 10. *In situ* Rhodium(I) complexes were prepared from chloro(1,5 - cyclooctadiene)rhodium(I) dimer [Strem Chemicals Inc.] according to the method described in Refs. 3, 10. (−) - (4R,5R)-DIOP, $[\alpha]_D^{25}$-11.9° (*C* 1.0, benzene) lit.[11] $[\alpha]_D^{25}$-12.3° (*C* 4.57, benzene), was purchased from Strem Chemicals Inc. and used as received. All new compounds gave satisfactory C, H and N microanalyses in accord with their molecular formulae [analyses performed at the Hebrew University of Jerusalem]. All m.ps are uncorrected. $^1$H NMR spectra were obtained on a Varian XL-100 spectrometer.

N-acylglycines (RCONHCH$_2$CO$_2$H, where R = i-Pr, t-Bu and 1-adamantyl) were prepared by Schotten-Bauman type[12] acylation of glycine and exhibited m.ps of 101–102° [R = i-Pr]; 127–128° [t-Bu]; and 161–162° [1-adamantyl]. Z-4-benzylidene - 2 - alkyl - 2 - oxazolin - 5 - one azlactones were synthesized from the appropriate N-acylglycines according to the method of Herbst and Shemin.[13] The m.ps, IR and $^1$H NMR spectra are listed in Table 3.

Z-α-acylaminocinnamic acids were prepared from the corresponding azlactones by hydrolysis according to the method of Carter and Risser,[14] and then were recrystallized from acetone/water. The m.ps, IR and $^1$H NMR spectra are listed in Table 4. The Z-methyl α-acylaminocinnamates were prepared from the corresponding acids via reaction with diazomethane.[15] Z-2,2,2 - Trifluoroethyl α-acetamidocinnamate was prepared from Z-4-benzylidene - 2 - methyl - 2 - oxazolin - 5 - one[13] via ring opening with 1 N sodium 2,2,2-trifluoroethoxide. The m.ps, IR and $^1$H NMR spectra of the Z-alkyl α-acylaminocinnamates are listed in Table 5.

Z-α-Benzamidocinnamic acid, m.p. 226–228° lit.[4] 223–226°; Z-methyl α-benzamidocinnamate, m.p. 143–145° lit.[16] 142–143°; Z-α-trifluoroacetamidocinnamic acid m.p. 193–195° lit.[7b] 196–199°; and Z-methyl α-trifluoroacetamidocinnamate, m.p. 80–81° lit.[7b] 79–80° are known compounds and were prepared according to the appropriate literature procedures, Z-methyl α-formamidocinnamate (m.p. 88–89°) was a gift of Prof. U. Schöllkopf. Z-α-formamidocinnamic acid (m.p. 185°) was obtained from the methyl ester via mild KOH-catalyzed hydrolysis.[17]

Optically-pure N - acyl - (S) - phenylalanine methyl esters were prepared from (S)-phenylalanine methyl ester hydrochloride, m.p. 153–154° and $[\alpha]_D^{25}$ + 35.0° (*C* 1.0, abs. EtOH) lit.[3] $[\alpha]_D^{25}$ + 34.8° (*C* 1.0, abs. EtOH) according to the general method described in Ref. 3. N - formyl - (S) - phenylalanine methyl ester was prepared by the method of Vigneaud *et al.*[18] N-trifluoroacetyl - (S) - phenylalanine methyl ester, $[\alpha]_D^{25}$ − 8.9° (*c* 2.0, abs. EtOH) lit.[19] $[\alpha]_D^{25}$ − 7.2° (abs. EtOH), was purchased from Sigma Chemical Co. The optical rotation in $CHCl_3$ soln was found to be: $[\alpha]_D^{25}$ + 100.0°; $[\alpha]_{434}^{25}$ + 224.0°; and $[\alpha]_{334}^{25}$ + 551.2° all at (*C* 1.0, $CHCl_3$). The m.ps, optical rotation, IR and $^1$H NMR spectra of the optically-pure standard compounds are listed in Table 6.

Table 3. Characterization of Z-4-benzylidene-2-alkyl-2-oxazclin-5-one Azlactones, $C_6H_5CH{=}\underline{C{-}N{=}C(R)OC}{=}O$

| R | m.p. | Infrared[a] | $^1$H nmr[b] | |
|---|---|---|---|---|
| i-Pr | 40-41° | 1760 (C=O s) | 7.99 ± 0.13 (m) | 2H-PhH |
| | | 1650 (C=N s) | 7.29 ± 0.09 (m) | 3H-PhH |
| | | | 7.01 (s) | 1H-PhCH |
| | | | 2.72 (septet) | 1H-CH(CH$_3$)$_2$, J 7 Hz |
| | | | 1.34 (d) | 6H-CH(CH$_3$)$_2$, J 7 Hz |
| t-Bu | 80-81° | 1780 (C=O s) | 7.99 ± 0.06 (m) | 2H-PhH |
| | | 1625 (C=N s) | 7.32 ± 0.07 (m) | 3H-PhH |
| | | | 7.03 (s) | 1H-PhCH |
| | | | 1.38 (s) | 9H-CH$_3$ |
| 1-Ada | 142-143° | 1760 (C=O s) | 7.99 ± 0.12 (m) | 2H-PhH |
| | | 1650 (C=N s) | 7.32 ± 0.11 (m) | 3H-PhH |
| | | | 7.03 (s) | 1H-PhCH |
| | | | 2.04 (broad s) | 9H-AdH |
| | | | 1.79 (broad s) | 6H-AdH |

[a] cm$^{-1}$, KBr pellet, s = stretching. [b] δ, $CDCl_3$/TMS, 100 MHz, m = multiplet, s = singlet, d = doublet. R = Me azlactone (m.p. 147–148°, vinylic proton 7.02 δ) undergoes ring opening to give methyl α-acetamidocinnamate (m.p. 125–127°) having Z-configuration, Ref. 4, 5.

Table 4. Characterization of Z-α-acylaminocinnamic acids, $C_6H_5CH=C(NHCOR)COOH$

| R | m.p. | Infrared[a] | $^1H$ nmr[b] | |
|---|---|---|---|---|
| i-Pr | 184-186° | 3200 (N-H,O-H s) | 7.30 ± 0.20 (m) | 7H-PhH, PhCH, NH |
| | | 1690 (C=O s, acid) | 3.55 ± 0.35 (m) | 1H-CH$(CH_3)_2$ |
| | | 1660 (C=O s, amide) | 1.38 (d) | 6H-CH$(CH_3)_2$,J 7 Hz |
| | | 1515 (N-H b) | | |
| t-Bu | 202-203° | 3300 (N-H,O-H s) | 7.74 (broad) | 1H-NH |
| | | 1690 (C=O s, acid) | 7.33 ± 0.17 (m) | 6H-PhH, PhCH |
| | | 1640 (C=O s, amide) | 1.26 (s) | 9H-$CH_3$ |
| | | 1500 (N-H b) | | |
| 1-Ada | 188-189° | 3500 (O-H s) | 7.24 ± 0.14 (m) | 6H-PhH, PhCH |
| | | 3340 (N-H s, sharp) | 6.11 (broad) | 1H-NH |
| | | 1695 (C=O s, acid) | 1.86 ± 0.14 (m) | 15H-AdH |
| | | 1640 (C=O s, amide) | | |
| | | 1500 (N-H b) | | |

[a]$cm^{-1}$, KBr pellet, s = stretching, b = bending. [b]δ, DMSO-$d_6$/TMS, 100 MHz, m = multiplet, s = singlet, d = doublet.

Table 5. Characterization of Z-alkyl α-acylaminocinnamates, $C_6H_5CH=C(NHCOR^2)COOR^1$

| $R^1$ | $R^2$ | m.p. | Infrared[a] | $^1H$ nmr[b] | |
|---|---|---|---|---|---|
| Me | i-Pr | 115-116° | 3230 (N-H s) | 7.30 ± 0.16 (m) | 6H-PhH, PhCH |
| | | | 1725 (C=O s,ester) | 6.78 (broad) | 1H-NH |
| | | | 1665 (C=O s,amide) | 3.79 (s) | 3H-$OCH_3$ |
| | | | 1525 (N-H b) | 2.51 (septet) | 1H-CH$(CH_3)_2$,J 7 Hz |
| | | | | 1.21 (d) | 6H-CH$(CH_3)_2$,J 7 Hz |
| Me | t-Bu | 101-102° | 3300 (N-H s) | 7.27 ± 0.23 (m) | 7H-PhH, PhCH, NH |
| | | | 1720 (C=O s,ester) | 3.76 (s) | 3H-$OCH_3$ |
| | | | 1660 (C=O s,amide) | 1.24 (s) | 9H-$CH_3$ |
| | | | 1505 (N-H b) | | |
| Me | 1-Ada | 136-137° | 3285 (N-H s) | 7.22 ± 0.14 (m) | 6H-PhH, PhCH |
| | | | 1715 (C=O s,ester) | 6.05 (broad) | 1H-NH |
| | | | 1635 (C=O s,amide) | 3.64 (s) | 3H-$OCH_3$ |
| | | | 1500 (N-H b) | 1.82 ± 0.16 (m) | 15H-AdH |
| $CH_2CF_3$ | Me | 150-151° | 3200 (N-H s) | 7.90 (broad) | 1H-NH |
| | | | 1730 (C=O s,ester) | 7.29 ± 0.15 (m) | 6H-PhH, PhCH |
| | | | 1665 (C=O s,amide) | 4.54 (q) | 2H-$OCH_2$,J 8.5 Hz |
| | | | 1520 (N-H b) | 2.06 (s) | 3H-$CH_3CO$ |

[a]$cm^{-1}$, KBr pellet, s = stretching, b = bending. [b]δ, $CDCl_3$/TMS, 100 MHz, m = multiplet, s = singlet, d = doublet, q = quartet.

Table 6. Characterization of N-acyl-(S)-phenylalanine methyl esters, $C_6H_5CH_2CH(NHCOR)COOCH_3$

| R | M.p. | $[\alpha]_\lambda^{25}$[a] | Infrared[b] | $^1$H nmr[c] | |
|---|---|---|---|---|---|
| H | 43-44° | +99.0[d] | 3200 (N-H s) | 8.06 (broad s) | 1H-formyl H |
| | | +225.1[e] | 1730 (C=O s,ester) | 7.27 ± 0.15 (m) | 5H-PhH |
| | | +564.4[f] | 1655 (C=O s,amide) | 6.70 (broad) | 1H-NH |
| | | | 1510 (N-H b) | 4.83 ± 0.10 (m) | 1H-CH |
| | | | | 3.61 (s) | 3H-$OCH_3$ |
| | | | | 3.04 (d) | 2H-$CH_2$Ph,J 7 Hz |
| i-Pr | 62-63° | +90.8[d] | 3330 (N-H s) | 7.04 ± 0.15 (m) | 5H-PhH |
| | | +206.3[e] | 1735 (C=O s,ester) | 5.77 (broad) | 1H-NH |
| | | +519.3[f] | 1645 (C=O s,amide) | 4.80 ± 0.10 (m) | 1H-CH |
| | | | 1545 (N-H b) | 3.66 (s) | 3H-$OCH_3$ |
| | | | | 3.08 (d) | 2H-$CH_2$Ph,J 6 Hz |
| | | | | 2.40 (septet) | 1H-$CH(CH_3)_2$,J 7 Hz |
| | | | | 1.09 (d) | 6H-$CH(CH_3)_2$,J 7 Hz |
| t-Bu | 84-85° | +73.5[d] | 3300 (N-H s) | 7.06 ± 0.14 (m) | 5H-PhH |
| | | +167.7[e] | 1740 (C=O s,ester) | 5.96 (broad) | 1H-NH |
| | | +430.8[f] | 1640 (C=O s,amide) | 4.80 ± 0.10 (m) | 1H-CH |
| | | | 1515 (N-H b) | 3.68 (s) | 3H-$OCH_3$ |
| | | | | 3.10 (d) | 2H-$CH_2$Ph,J 7 Hz |
| | | | | 1.14 (s) | 9H-$CH_3$ |
| 1-Ada | 101-102° | +63.7[d] | 3320 (N-H s) | 7.00 ± 0.06 (m) | 5H-PhH |
| | | +143.5[e] | 1710 (C=O s,ester) | 5.95 (broad) | 1H-NH |
| | | +358.7[f] | 1630 (C=O s,amide) | 4.82 ± 0.14 (m) | 1H-CH |
| | | | 1525 (N-H b) | 3.70 (s) | 3H-$OCH_3$ |
| | | | | 3.10 (d) | 2H-$CH_2$Ph,J 7 Hz |
| | | | | 1.87 ± 0.13 (m) | 15H-AdH |

[a] $10^{-1} \times [\alpha]$ = degree $g^{-1}$ $cm^2$, KBr pellet, s = stretching, b = bending. [c] δ, $CDCl_3$/TMS, 100 MHz, m = multiplet, s = singlet, d = doublet. [d] λ = sodium-D (589 nm). [f] λ = 334.15 nm.

The work-up of the hydrogenation experiments and the polarimetric determination of the reduction product optical purity was performed as described in Ref. 20 [with the exception of the N-trifluoroacetylphenylalanine and N-acetylphenylalanine 2,2,2-trifluoroethyl ester products]. All free acid reduction products were directly converted to the methyl esters via diazomethane as described in Ref. 20. The validity of the optical purity determination of the methyl esters (from the free acid products plus diazomethane) has been shown in Ref. 20.

*Determination of optical purity of the N-trifluoroacetylphenylalanine product.* As described in Ref. 20, the crude free acid product mixture was treated with diazomethane and then chromatographed on a silica-gel column. The purified N-trifluoroacetylphenylalanine methyl ester was then analyzed by gas chromatography using a column with a 5% loading of N - lauroyl - (S) - valine 2 - methyl - 2 - heptadecylamide on Chromosorb P (acid-washed, DMCS coated, 80–100 mesh); 60 ml/min He flow rate, 1/8-in. diam. and 3.0 m column length. Using a column temp. of 170°, the retention times of the (R) and (S)-enantiomers of N-trifluoroacetylphenylalanine methyl ester were found to be 48.0 and 50.7 min, respectively, using the appropriate standard compounds. The ratio of peak areas of the (R): (S)-enantiomers was found to be 58:42 which represents a 16% enantiomeric excess of the (R)-enantiomer.

*Determination of optical purity of the N-acetylphenylalanine 2,2,2 - trifluoroethyl ester product.* The purified N-acetylphenylalanine 2,2,2 - trifluoroethyl ester product, $[\alpha]_D^{25}$ − 22.6° (*C* 1.21, $CHCl_3$), was converted to the corresponding methyl ester via acid-catalyzed transesterification according to the method described in Ref. 3. After silica-gel column chromatography, the purified N-acetylphenylalanine methyl ester gave $[\alpha]_D^{25}$ − 52.9° (*c* 1.0, $CHCl_3$) for 52% ee-(R), based upon $[\alpha]_D^{25}$ + 101.3° (*c* 1.0, $CHCl_3$) for the pure (S)-enantiomer.

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