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Chirospecific synthesis of D and L *p*-chlorohomophenylalanine N-t-BOC DCHA salts*

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Summary. The chirospecific conversions of D-glucosamine hydrochloride and D-mannosamine hydrochloride to the configurationally stable L and D isomers of N-*t*-butyloxycarbonylserinal were carried out by *t*-butylcarbonylation followed by sodium borohydride reduction and sodium meta-periodate oxidation. Reaction of the L and D aldehydes with the Wittig reagent prepared from 4-chlorobenzyltriphenylphosphonium chloride and butyl lithium followed by catalytic hydrogenation, Jones oxidation and salt formation with dicyclohexylamine gave the DCHA salts of the D and L isomers of *p*-chlorohomophenylalanine N-*t*-Boc in high enatiomeric excess. The optical purity of the title compounds was established by hydrolysis to the respective free amino acids, followed by chiral derivatization and HPLC analysis.

Keywords: Amino acids – Chirospecific – D-Glucosamine hydrochloride – D-Mannosamine hydrochloride – L-N-t-Butyloxycarbonylserinal – D-N-*t*-Butyloxycarbonylserinal – D-*p*-Chlorohomophenylalanine N-*t*-Boc DCHA salt – L-*p*-Chlorohomophenylalanine N-*t*-Boc DCHA salt

Introduction

Since the isolation and characterization of Gonadotropin-releasing hormone (GnRH) in 1971, thousands of analogs have been synthesized and tested for contraceptive activity (Folkers et al., 1983; Karten, 1986). Some of these have proved to cause complete inhibition of ovulation in animals in doses as low as

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one microgram (Ljungqvist et al., 1990). Current research on the synthesis of GnRH antagonists has focused on the replacement of the natural amino acids of the native sequence with synthetic unnatural analogues. Continued research in this field neccesitates a constant supply of these unnatural amino acids as well as ongoing investigations of new synthetic methodologies.

One of the newer strategies of asymmetric amino acid synthesis involves the use of protected serinal derivatives for homologation to new amino acids (Williams, 1989). In a recent publication, (Giannis and Henk, 1990) a method for the chirospecific preparative synthesis of novel unnatural amino acids from N-protected D and L serinal derived from readily available sugars was developed. We have simplified this procedure and extended its scope to include other types of amino acids. Presented are the details of the synthesis of the D and L isomers of *p*-chlorohomophenylalanine-N-*t*-BOC dicyclohexylamine salt.

Methods and materials

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Proton-NMR spectra were recorded on a Varian EM-390 (90 MHz) spectrometer in deuterochloroform ($CDCl_3$) as solvent unless noted otherwise and using tetramethylsilane (TMS) as an internal standard ($\delta = 0.0$). Infared spectra were recorded on a Perkin Elmer Model 1600 FT-instrument equipped with a diffuse reflectance accessory using a potassium bromide (KBr) matrix. Optical rotations were measured on a Rudolph Research Autopol II automatic polarimeter using a 1.0 dm cell. Mass spectral analyses$^{(EI)}$ were conducted by Dr. Susan Weintraub of the University of Texas Health Science Center at San Antonio using a Finnigan-MAT model 4615. Combustion analyses were performed by Midwest MicroLabs, Ltd., Indianapolis, Indiana. "Dry column" chromatography was performed on Woelm silica in a nylon column (Loev and Goodman, 1970). TLC Analyses were carried out on silica gel GF (Analtech) glass plates (2.5 × 10 cm with 250 μM layer and prescored).

Most chemicals and solvents were analytical grade and used without further purification. Some reagents, such as tetrahydrofuran (THF), dioxane, dicyclohexylamine and triethylamine were purified by standard laboratory procedures. D-Glucosamine hydrochloride and D-mannosamine hydrochloride were purchased from Aldrich Chemical Company, Milwaukee, WI. Di-*tert*-butyl dicarbonate was purchased from Fluka Chemical Corp., Hauppauge, NY. 4-Chlorobenzyltriphenylphosphonium chloride was purchased from MTM Research Chemicals (Lancaster Synthesis Inc.), Windham, NH.

Analytical HPLC analyses were conducted using a Waters HPLC system equipped with a model 6000A pump, model U6K injector, Model 1481 variable wavelength detector, and model 730 data module.

Experimental

D-Glucosamine-N-Boc (**2a**)

D-glucosamine hydrochloride (**1a**, 5.0 g, 23.2 mmol) was dissolved in water (23 mL). Absolute ethanol (23 mL) was added followed by di-*t*-butyldicarbonate (8.0 g, 36.7 mmol). The reaction was stirred at 40 °C for 3 min and triethylamine (3.6 mL, 25.8 mmol) was added. The mixture was then stirred at 40–41 °C for 1.5 hr. At the end of that time, some of the product had precipitated out. The suspension was cooled to 5 °C and the product was collected by filtration. The precipitate was washed with a small amount of cold ethanol (1x) and ether (2x). Drying *in vacuo* gave white crystalline product (**2a**. 5.1 g, 75%); mp 192–193 °C (d) [Lit. 190–191 °C, Pozdnev, 1980].

$[\alpha]_D^{25} = +65.5°$ (c = 1.01, methanol) [Lit. $[\alpha]_D^{20} = +65.5°$ Pozdnev, 1980].

NMR (D_6-DMSO + $CDCl_3$) δ 1.37(s, 9 H, O—C(CH_3)), 3.23(m. 2 H, CH_2OH), 4.67 and 5.13(m, 1 H, C*H*—NH), 5.55 and 6.23(m, 1 H, NH) ppm.

D-Mannosamine-N-Boc (**2b**)

D-Mannosamine hydrochloride (**1b**, 20 g., 92.7 mmol) was derivatised using di-*t*-butyldicarbonate (32 g, 146.6 mmol) and triethylamine (15 mL, 107.6 mmol) in water (100 mL) and ethanol (100 mL) by the same procedure used for compound (**1a**). This material did not precipitate out. The ethanol was removed in vacuo under a stream of nitrogen and the aqueous solution was extracted with hexanes (3x) to remove excess di-*t*-butyldicarbonate. The hexanes extracts were back extracted once with water and the combined aqueous fractions were concentrated *in vacuo* at 40–50 °C to give the crude product (**2b**) as a clear syrup. This material was used directly in the subsequent reaction without further purification. The proton NMR of this material was not readily distinguishable from that obtained for (**2a**).

N-tert-Butyloxycarbonyl-L-serinal (**4a**)

Glucosamine N-Boc (**2a**, 5 g, 17.9 mmol) was dissolved in 75% ethanol (150 mL). A solution of sodium borohydride (5 g, 132 mmol) in 75 % ethanol (50 mL) was added and the reaction mixture was stirred at room temperature overnight. The ethanol was removed *in vacuo* under a stream of nitrogen and the residue was diluted to 150 mL with water. The solution was carefully adjusted to a pH of 6.5 with glacial acetic acid and the mixture was stirred at room temperature for 30 min. The solution was adjusted to a pH of 7.0 with 4N NaOH and the mixture was cooled to 5 °C in an ice bath. A solution of sodium meta-periodate (11.9 g, 55.6 mmol) in water (100 mL) was added dropwise and the solution was stirred at 5 °C for 1.5 hr. The mixture was extracted with ether (9x) and the organic fractions were washed with water (1x) and brine (1x). The organic extracts were combined, dried over sodium sulfate, filtered and concentrated in vacuo to give 3.2 g of a stable foam. This material was used directly in the subsequent reaction without further purification.

N-tert-Butyloxycarbonyl-D-serinal (**4b**)

The crude mannosamine N-Boc (**2b**, assume 92.7 mmol) in absolute ethanol (600 mL) and water (200 mL) was reacted with a solution of sodium borohydride (20 g, 529 mmol) in 75% ethanol (200 mL) by the same procedure used for compound (**2a**). The intermediate work-up followed by dilution to a volume of 500 mL with water, pH adjustment and reaction with sodium meta-periodate (61.5 g, 287.5 mmol) in water (500 mL) were carried out in a similar manner as that given for compound (**4a**). Identical workup gave 9.7 g of product (**4b**) as a stable foam. The NMR of this material was identical to that obtained for compound (**4a**).

N-tert-Butyloxycarbonyl-3(R)-amino-1-(4'-chlorophenyl)but-1-en-4-ol (**5a**)

Under nitrogen and anhydrous conditions, 4-chlorobenzyltriphenylphosphonium chloride (12.3 g, 29.1 mmol) was suspended in dry tetrahydrofuran (300 mL). The mixture was cooled to 0 °C in an ice bath and was treated dropwise with a solution of *n*-butyllithium in hexanes (1.25 M, 23 mL, 28.7 mmol) added via syringe. The resultant red-brown suspension was stirred at 0 °C for thirty minutes. A solution of the aldehyde (**4a**, 5.0 g, 26.4 mmol) in dry THF (200 mL) was added dropwise and the reaction was stirred at 0 °C for one hour. The solvent was removed *in vacuo* under a stream of dry nitrogen and the residue was purified via dry column chromatography (ethyl acetate/hexanes 1:1) to give a mixture of the *Z* and *E* isomers of the expected Wittig adduct (**5a**, 4.8 g, 61%); mp 100–109 °C.

FTIR (KBr, diffuse reflectance) ν_{max} 3482, 3375, 2985,1669, and 1531 cm^{-1}.

NMR ($CDCl_3$) δ 1.4 and 1.46(two singlets, 9 H, *t*-butyl), 3.72(m, 2 H, CH_2OH), 4.4 (br.m., 1 H, CH—NH), 5.5(m, 1 H, NH), 5.6–6.8(m, 2H, olefinic), 7.3(s, 4 H, aromatic) ppm.

Analysis: Calc'd for $C_{12}H_{20}NO_3Cl$, C 60.50; H 6.77; N 4.70; Cl 11.91

Found: C 60.40; H 6.89; N 4.97; Cl 11.65.

N-tert-Butyloxycarbonyl-3(S)-amino-1-(4'-chlorophenyl)but-1-en-4-ol **(5b)**

Following the same procedure given for compound (**5a**), the ylid obtained from the reaction of 4-chlorobenzyltriphenylphosphonium chloride (12.3 g, 29.1 mmol) in THF (300 mL) and 1.15 M *n*-butyllithium in hexanes (26 mL, 29.9 mmol) was reacted with the aldehyde (**4b**, 5.0 g, 26.4 mmol) in THF (200 mL). Identical work-up and purification gave a similar mixture of the *Z* and *E* isomers of compound (**5b**, 5.2 g, 66%); mp 101–110 °C.

FTIR and NMR identical to those obtained for (**5a**).

Analysis: Calc'd for $C_{12}H_{20}NO_3Cl$, C 60.50; H 6.77; N 4.70; Cl 11.91

Found: C 60.46; H 6.74; N 4.71; Cl 11.81.

N-tert-Butyloxycarbonyl-2(R)-amino-4-(4'-chlorophenyl)butan-1-ol **(6a)**

Platinum oxide (0.4 g, 1.76 mmol) was suspended in absolute ethanol (100 mL) in a 500 mL flask connected to a hydrogen cylinder by means of a manometer for measurement of hydrogen uptake. The system was flushed with hydrogen and the manometer was charged with hydrogen. The catalyst was reduced with vigorous stirring to a constant manometer reading. A solution of the phenylallylamino alcohol (**5a**, 4.1 g, 13.8 mmol) in ethanol (100 mL) was then introduced via syringe. Hydrogen uptake occurred with vigorous stirring and was monitored by means of the manometer. The manometer gave a constant reading after two hours and an uptake of 1.1 equivalents of hydrogen had occurred. The reaction mixture was filtered through Celite and the solvent was removed *in vacuo*. Crystallization of the residue from ether/pentane gave the pure amino alcohol (**6a**, 3.0 g, 73%); mp 87–89 °C.

$[\alpha]_D^{25} = +8.98°$ (c = 1.00, ethanol).

FTIR (KBr, diffuse reflectance) ν_{max} 3371, 3316, 2934, 1683, and 1511 cm^{-1}.

NMR ($CDCl_3$) δ 1.43(s, 9 H, *t*-butyl), 1.83(b.m. 2 H, $CH-CH_2-CH_2-Ph$), 2.67(m, 2 H, OH and CH–NH), 3.63(b.s., 2 H, CH_2OH), 7.25(m, 4 H, aromatic) ppm.

MS(M/e): 243 (M^+-*t*Bu).

Analysis: Calc'd for $C_{15}H_{22}NO_3Cl$, C 60.10; H 7.48; N 4.67; Cl 11.83

Found: C 60.21; H 7.59; N 4.67; Cl 11.72

N-tert-Butyloxycarbonyl-2(S)-amino-4-(4'-chlorophenyl)butan-1-ol **(6b)**

With the exception of the choice of solvent, compound (**5b**, 1.0 g, 3.36 mmol) was reduced using platinum oxide (0.1 g, 0.44 mmol) in dioxane (80 mL) following the procedure given for compound (**5a**). Identical workup gave the *S* isomer (**6b**, 0.84 g, 83%); mp 91–93 °C.

$[\alpha]_D^{23} = -8.98°$ (c = 1.00, ethanol).

FTIR, NMR and MS identical to those obtained for compound (**6a**).

Analysis: Calc'd for $C_{15}H_{22}NO_3Cl$, C 60.10; H 7.48; N 4.67; Cl 11.83

Found: C 60.48; H 7.44; N 4.58; Cl 11.50

D-p-Chlorohomophenylalanine-N-t-Boc (**7a**)

A magnetically stirred solution of alcohol (**6a**, 1.5 g, 5.04 mmol) in acetone (30 mL) was treated dropwise with Jones reagent (2.7 M CrO_3, 2.2 M H_2SO_4) at room temperature until a persistence of a brown-yellow color was observed. The reaction was stirred an additional 5 minutes at room temperature and then was treated dropwise with isopropanol until the reaction color turned green. The mixture was diluted to 200 mL with water and extracted with ethyl acetate (3x). The organic fractions were washed with water (1x), brine (1x), combined, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the N-Boc amino acid (**7a**, 1.0 g, 64%) as an oil.

$[\alpha]_D^{25} = -6.67°$ (c = 2.7, ethanol).

FTIR (KBr, diffuse reflectance) ν_{max} 2981, 2558, and 1717 cm^{-1}.

NMR ($CDCl_3$) δ 1.4(s, 9H, t-butyl), 2.07(m, 2 H, CH–CH_2–CH_2Ph), 2.67(m, 2 H, benzyl CH_2), 4.3(b.m., 1 H, α-CH), 7.2 (m, 4 H, aromatic), 10.4 (b.s., 1 H, COOH) ppm.

L-p-Chlorohomophenylalanine-N-t-Boc (**7b**)

The alcohol (**6b**, 2.5 g, 8.4 mmol) in acetone (50 mL) was oxidized with Jones reagent following the procedure given for compound (**6a**). Normal work-up gave the L isomer (**7b**, 1.8 g, 69%).

FTIR and NMR identical to those obtained for compound (**7a**).

D-p-Chlorohomophenylalanine (**8a**)

A solution of the N-Boc (**7a**, 0.34 g, 1.07 mmol) in trifluoroacetic acid (10 mL) and water (1 mL) was stirred at room temperature for two hours. The solvents were concentrated in vacuo under a stream of nitrogen and the residue was suspended in water (50 mL). The pH of the suspension was adjusted to 5.8 with 10% NH_4OH solution and the precipitate was collected by filtration and washed with water, acetone and ether. Drying in vacuo gave the free amino acid (**8a**, 0.18 g); mp 270–271 °C (d);

$[\alpha]_D^{26} = -42.4°$ (c = 1.0, 1 N HCl);

FTIR (KBr, diffuse reflectance) ν_{max} 2925, 1582 and 1520 cm^{-1}.

NMR ($CDCl_3$ + CF_3COOH) δ 2.39(m, 2 H, β-CH_2), 2.8(m, 2 H, benzyl CH_2), 4.23(b.s., 1 H, α-CH), 7.2 (m, 7H, aromatic + NH_3) ppm.

MS (M/e): 213 (M^+).

HPLC analysis of the GITC derivative of compound (**8a**) prepared according to the procedure of Kinoshita et al [8, 9] indicated an optical purity of 94% ee (Whatman Partisil 5 ODS-3, 65% MeOH/35 % 0.05 M KH_2PO_4 buffer, pH 3.0 with $HClO_4$; 0.9 ml/min; λ = 250 nm).

L-p-Chlorohomophenylalanine (**8b**)

Following the same procedure carried out for compound (**8a**), the L-N-Boc compound (1.21 g, 3.86 mmol) was hydrolysed in trifluoroacetic acid (30 mL) and water (1 mL) to give the free amino acid (**8a**, 0.64 g); mp 285–287 °C (d, sealed tube);

$[\alpha]_D^{24} = +45.9°$ (c = 1.00, 1 N HCl);

FTIR, MS, and NMR identical to those obtained for (**8a**)

Analysis: Calc'd for $C_{10}H_{12}NO_2Cl$, C 56.21; H 5.66; N 6.56; Cl 16.59

Found: C 56.45; H 5.79; N 6.54; Cl 16.53.

HPLC Analysis of the GITC derivative of compound (**8b**) indicated an optical purity of 98.4% ee.

D-p-Chlorohomophenylalanine-N-t-Boc DCHA Salt **(9a)**

A solution of p-chlorohomophenylalanine N-t-Boc (**7a**, 1.3 g, 4.14 mmol) in anhydrous ether (15 mL) was treated with freshly distilled dicyclohexyamine (0.9 mL, 4.5 mmol). The mixture was stirred at room temperature for 30 min. and then concentrated *in vacuo* under a stream of dry nitrogen. The residue was crystallized from hot acetonitrile to give the pure salt (**9a**, 1.5 g, 73%); mp 143–154 °C;

$[\alpha]_D^{27} = -18.9°$ (c = 1.00, ethanol);

FTIR (KBr, diffuse reflectance) ν_{max} 3400, 2937, 2859, 1706 and 1631 cm^{-1}.

NMR ($CDCl_3$) δ 1.44(s, 9 H, *t*-butyl), 4.07(m, 1 H, α-CH), 5.55(b.d., 1 H, NH), 7.22(m, 4 H, aromatic) ppm.

Analysis: Calc'd for $C_{27}H_{43}N_2O_4Cl$, C 65.60; H 8.75; N 5.66; Cl 7.16

Found: C 65.64; H 8.76; N 5.64; Cl 6.91.

L-p-Chlorohomophenylalanine-N-t-Boc DCHA Salt **(9b)**

Following the same procedure used for preparing compound (**9a**), a solution of the L-N-Boc (**7b**, 0.5 g, 1.59 mmol) in ether (10 mL) was reacted with dicyclohexylamine (0.35 mL, 1.76 mmol) to give the L-DCHA salt (9b, 0.66 g, 84%); mp 141–151 °C;

$[\alpha]_D^{24} = +20.2°$ (c = 1.00, ethanol);

FTIR and NMR identical to those obtained for compound (**9a**).

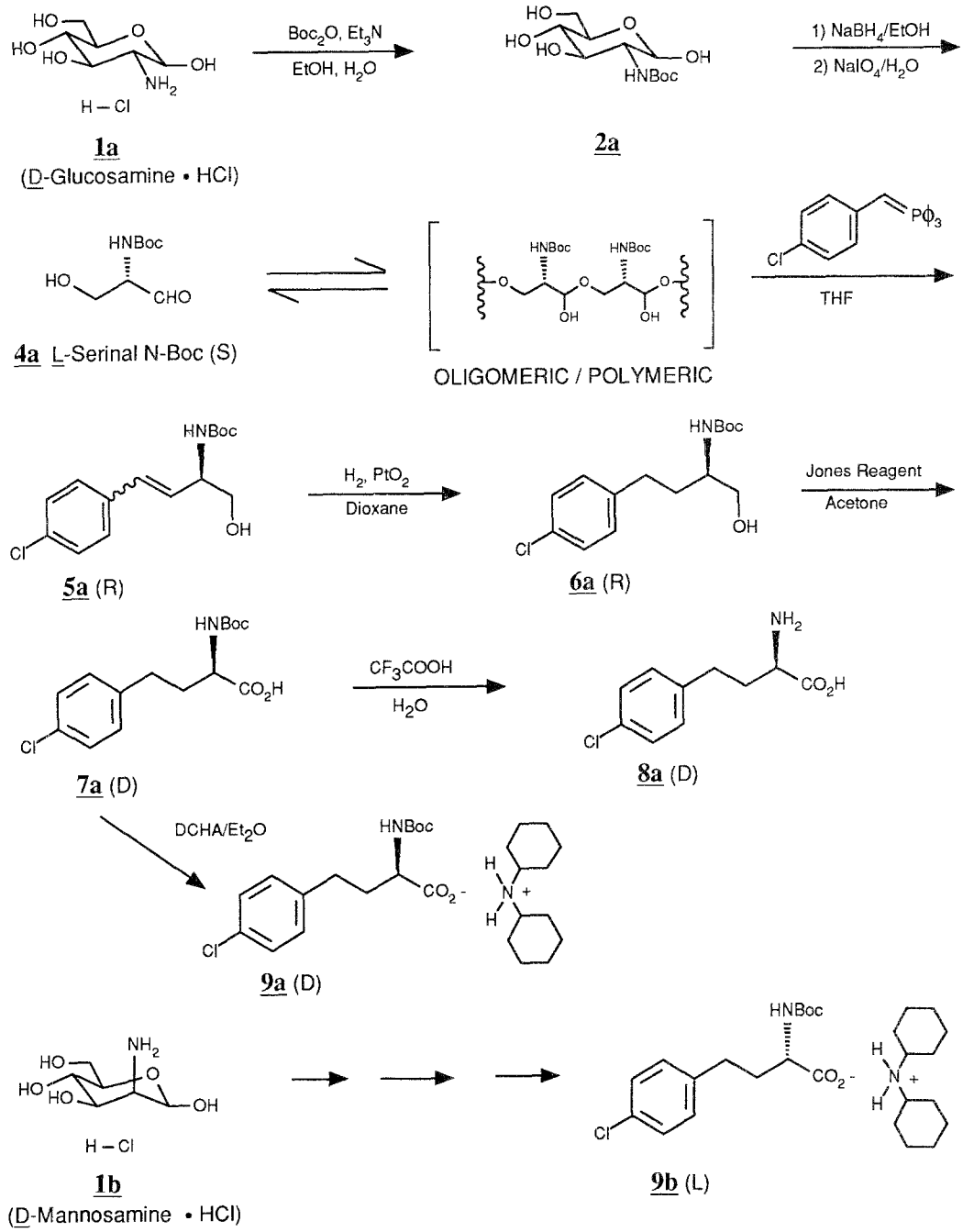
Analysis: Calc'd for $C_{27}H_{43}N_2O_4Cl$, C 65.60; H 8.75; N 5.66; Cl 7.16

Found: C 65.59; H 8.80; N 5.63 Cl 7.17.

Results and discussion

The method we employed for the synthesis of the D and L isomers of *p*-chlorohomophenylalanine N-*t*-Boc is a modification of one recently developed (Giannis and Henk, 1990) and is outlined in Scheme 1. The starting material for the D isomer, D glucosamine hydrochloride (**1a**) was converted to the N-*tert*-butyloxycarbonyl derivative (**2a**) by reaction with di-*t*-butyldicarbonate and triethylamine in aqueous ethanol according a published procedure [Pozdnev (1980)]. Reduction of (**2a**) with excess sodium borohydride followed by oxidation with sodium meta-periodate gave the N-*tert*-butyloxycarbonyl-L-serinal (**4a**) in 70% overall yield from (**1a**). In a similar manner, N-*tert*-butyloxycarbonyl-D-serinal (**4b**) was obtained in 72% overall yield starting from D mannosamine hydrochloride (**1b**).

According to the literature (Giannis and Henk, 1990), the aldehydes are obtained as mixtures of the free aldehyde in equilibrium with an oligomeric/polymeric form, perhaps in the form of a poly(hemiacetal) as is shown in scheme I. Our NMR data is consistent with this hypothesis in that the *t*-butyl absorbence ($\sim$1.4 ppm) appears as a multiplet and the aldehyde absorbence ($\sim$8.1 ppm)



Scheme 1

integrates to less than one proton. However, these spectral observations are not sufficient to determine the exact stuctural details of these materials or to preclude other possibilities. No evidence of oxidation or racemization of compounds (**4a**) and (**4b**) could be detected after storage of several days under ambient conditions.

In the published procedure (Giannis and Henk, 1990), compound (**4a**) was reacted with a number of phosphorous ylids stabilized in the α position with a

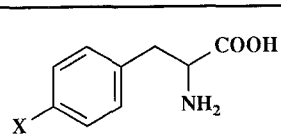
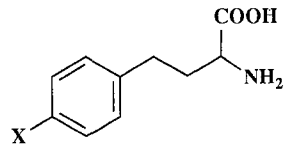
carbonyl group to give a variety of allylamino alcohols functionalized with a carbonyl group at the δ position. We have extended the scope of this reaction by the reaction of (**4a**) and (**4b**) with the semistabilized ylid prepared from 4-chlorobenzyl triphenylphosphonium choride and butyllithium to give the phenylallylamino alcohols (**5a**) and (**5b**) in 61% and 66% yields respectively. Hydrogenation of the phenylallylamino alcohols was carried out using platinum oxide as catalyst at a pressure of one atmosphere. The choice of solvent for this reaction can be critical. Whereas reduction of (**5a**) using ethanol as solvent gave the saturated γ-phenyl amino alcohol (**6a**) in 73% yield with no detectable hydrogenolysis of the chlorine, the same reaction carried out on (**5b**) gave product (**6b**) contaminated with 10% of the dechlorinated derivative. The use of the less polar solvent dioxane gave an 80% yield of (**6b**) with no detectable hydrogenolysis.

In the original paper (Giannis and Henk, 1990), the final oxidation to give the amino acid-Boc products was carried out using ruthenium tetroxide catalysis (Carlsen et al., 1981). This procedure is unsuitable for compounds (**6a**) and (**6b**) due to the fact that ruthenium tetroxide is also capable of oxidizing aromatic rings to carboxylic acids (Carlsen et al., 1981). The successful oxidation of alcohols (**5a**) and (**5b**) was carried out using Jones reagent at room temperature to give the N-Boc protected amino acids (**7a**) and (**7b**) as oils in 64% and 69%, respectively. For purification and ease of handling, compounds (**7a**) and (**7b**) were converted to their respective dicylohexylamine salts (**9a** and **9b**) in 73% and 84% yields.

The assessment of the optical purity of compounds (**7a**) and (**7b**) was carried out by hydrolysis to the respective free amino acids (**8a** and **8b**) followed by derivation with 2,3,4-tetra-O-acetyl-β-D-glucopyranosyl isothiocyanate (GITC) and analysis by HPLC (Kinoshita, 1981; Nimura, 1980). The results of this analysis gave 94% ee for compound (**8a**) and 98.4% ee for compound (**8b**).

It is of interest to note that the rotation of compounds (**8a**) and (**8b**) are of opposite sign to the corresponding isomers of *p*-chlorophenylalanine. This sign reversal upon homologation of phenylalanine to homophenylalanine has been documented [Weller (1982)]. These observations are summarized in Table 1.

Table 1. Optical rotation sign reversal upon homologation of phenylalanines

X		
H	L - 8.97 D + 8.97	L + 44.9 D - 43.3
Cl	L - 2.50 D + 3.94	L + 45.9 D - 42.4

c=1.00(1N HCl)

All rotations measured at Southwest Foundation for Biomedical Research.

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