Stereoselective Synthesis of Stable Isotope-Labeled L-α-Amino Acids: Electrophilic Amination of Oppolzer's Acyl Sultams in the Synthesis of L-[^{15}N]Alanine, L-[^{15}N]Valine, L-[^{15}N]Leucine, L-[^{15}N]phenylalanine and L-[1-^{13}C, ^{15}N]Valine.

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SUMMARY

Using 1-chloro-1-[^{15}N]nitrosocyclohexane, we have prepared five L-[α-^{15}N]amino acids. The stereoselective electophillic hydroxyamination of (*S*)-acylbornane-10,2-sultams, followed by Zn^0/H^+ reduction, and alkaline cleavage of the chiral auxiliary, gave the amino acids in 97.2-99.5 % e.e. By starting with labeled (*S*)-acylbornane-10,2-sultams this stereoselective route could be to prepare many ^{13}C and/or ^{15}N isotopomers of α-amino acids.

Keywords: 1-chloro-1-[^{15}N]nitrosocyclohexane, L-[^{15}N]alanine, L-[^{15}N]valine, L-[^{15}N]leucine, L-[^{15}N]phenylalanine L-[1-^{13}C,^{15}N]valine, bornane-10,2-sultam, and camphor-10-2-sultam

INTRODUCTION

Stable isotope-labeled amino acids are required for studies of amino acid metabolism and for studies of peptide and protein structure and dynamics. Racemic mixtures of ^{15}N-labeled amino acids have been made by the Gabriel synthesis which involves the nucleophilic displacement of an appropriate α-bromocarboxylic acid with potassium [^{15}N]phthalimide[1]. The Strecker synthesis is also useful for α-amino labeling[2]. Finally Yuan and Ajami[3,4] described a procedure for making N-acetylamino acids from [^{15}N]acetamide. For many applications, the naturally occurring L-configuration of the labeled amino acid is necessary; therefore, the above methods require the resolution of enantiomers. We have been interested in developing stereoselective methods for incorporating stable isotopes into L-amino acids[5-8]. The remarkable stereoselectivity and versatility of the strategies for the syntheses of L- or D-amino acids developed by

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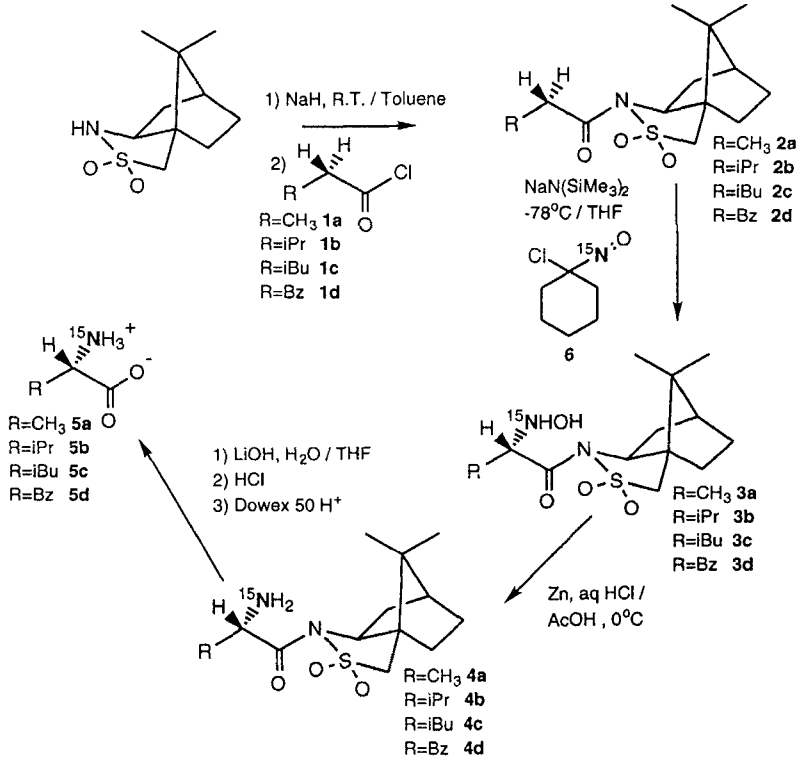
Oppolzer and coworkers[9-13] attracted our attention. This manuscript reports our first attempts to apply Oppolzer's methods to the stereoselective synthesis of L-[α-^{15}N]amino acids. Specifically we report the use of 1-chloro-1-[^{15}N]nitrosocyclohexane[14] in the synthesis of ^{15}N-labeled L-amino acids (Scheme 1).



Scheme 1) Synthesis of ^{15}N-Labeled L-α-Amino Acids

Results and Discussion

Oppolzer and coworkers[9-11] have developed a strategy for the synthesis of amino acids which involves the enantioselective generation of the C-α stereocenter by introduction of the amino group. Acyl groups are linked to the Oppolzer chiral auxiliary as amides by treatment of bornane-10,2-sultam with acyl chlorides (**1a**-**1d**). Acyl bornane-10,2-sultams (**2a**-**2d**) are converted to the corresponding enolates using sodium *bis*(trimethysilyl)amide. Titration of the enolates with a solution of 1-chloro-1-[^{15}N]nitrosocyclohexane (**6**) yields sultam-linked N-hydroxy-α-[^{15}N]amino acids (**3a**-**3d**). Reduction with Zn°/H^{+} affords the sultam linked amino acids (**4a**-**4d**). Acid hydolysis of the amide linkage frees the corresponding α-amino acids with very high overall enantioselectivity.

Oppolzer and coworkers[9-11] carefully purified all intermediates outlined above. However, in our hands there was no significant effect on yield if purification of the intermediates was not done. Of course, chromatographic purification and crystallization of the intermediates has the predicited effect of increasing the overall enanatiomeric excess (e.e.) to the reported level of >99.7% Without intermediate purification, we observed e.e.s of 97.2 to 99.5% in our product L-amino acids.

We differ significantly in our chemistry in two ways. We have prepared the natural 2*S* enantiomers with label, while in general Oppolzer and coworkers[9-11] prepared the 2*R* isomers. In addition, we developed conditions for preparing the acyl sultams that are more efficient for labeling. We found that by using an excess of sultam, which was recovered, our yields of acyl sultams in some individual preparations was nearly quantitative, apparently depending on the purity of the acid chlorides. A simple aqueous base wash to remove the excess sultam gave products which, after workup, had one degree melting ranges without any further purification. Recovery of the sultam from the base washes was straightforward. This reactant ratio is inverse to that reported by Oppolzer and coworkers[9-11] and increases the yield of the acyl sultams in terms of the acyl chlorides. This is important because labeled acyl chlorides are more expensive than the sultam.

In our hands the reduction of the hydroxyamines (**3a**-**3d**) to the amines with Zn°/HCl/HOAc was problematical. The hydroxyamines were unstable to racemization and to other degradation over time. It became our practice to immediately reduce these intermediates to avoid significant decreases in the enantiomeric purity of the products. For a variety of reasons, we experienced great variations in the reduction yields . We found that it was imperative that this system be kept ice-cold with an efficient heat sink, such as an ice bath. When we attempted the reduction of several hydroxyaminesultams at 3°C in a cold room with cooling only by circulating ambient air, we observed significant amounts of cleavage of the amino acid from the sultam. For example, the reduction of the hydroxyamine leading to alanine resulted in complete cleavage. The separation of a small amount of amino acid from a large amount of Zn^{+2} was tedious and not very successful. Proper continuous vigorous magnetic stirring was also important so as to avoid local heating and concomitant cleavage of the sultam moiety. In two cases of

inefficient stirring, the zinc powder inexplicably prilled, thereby occluding product and starting material.

Methods

Chemicals- 1-Chloro-1-[15N]nitrosocyclohexane was prepared as described[14]. [1-^{13}C]isovaleroyl chloride was prepared by $SOCl_2$ treatment of [1-^{13}C]isovaleric acid, which was prepared by $^{13}CO_2$ treatment of isobutyl magnesium bromide (Aldrich Chemical Co.). (2*S*)-Camphor-10,2-sultam ((2*S*)-bornane-10,2-sultam) was purchased from Oxford Asymmetry Ltd. (Abingdon/UK). THF was distilled from K°/benzophenone. Evaporation was done with Büchi rotary evaporators evacuated by direct-drive mechanical pumps preceded by a trap cooled in liquid nitrogen. Ion exchange on Dowex™ AG50X8 H^+ 200-400 mesh (Bio-Rad Laboratories, Inc.) was used to convert the amino acids to their zwitterions[7].

Analytical Methods- Melting points were determined using a Thomas-Hoover apparatus and are uncorrected. Melting points are compared to that of the unlabeled enantiomers[10].

Proton-decoupled ^{13}C FT-NMR spectra were obtained at 50.3 MHz using a Bruker AM-200 WB NMR spectrometer. Acquisition parameters were as follows: 10.869 KHz sweep width, 16 K data points, 0.75 s acquisition time, 2 s relaxation delay, 0.663 Hz/pt data point resolution, and 25°C. For the determination of isotopic enrichments, signal intensities were determined by Lorentzian line shape analysis. Chemical shifts are reported in ppm using the solvent as an internal reference ($CDCl_3$ = 77.0 ppm). The chemical shifts of the unlabeled enantiomers of many of the sultam derivatives have been reported[10].

The enantiomeric purity of the product amino acids was determined by gas chromatography (Hewlett-Packard 5890A GC) using a fused silica capillary column (25 meter) with a chiral stationary phase (Chirasil-Val III, Alltech Associates). The amino acids were chromatographed as their N-trifluoroacetylamide n-propyl esters[15] and monitored using a flame ionization detector. Calibration samples of the D, L, and DL amino acids were prepared from commercially available amino acids. Enantiomeric excess (e.e.) was calculated from the integrated areas (Hewlett-Packard 3396 Series II

integrator) of the peaks of the D- and L- isomers as follows: e.e. = (L-D)/(L+D). At first we believed our products to have e.e.s of 100%, since in no case did we observe a peak having a retention time similar to that of the known D-amino acid standards. However, it was obvious that there was always a small peak ahead of the main L-peak in the chromatogram. We resolved this by spiking our experimental samples with a small amount (to give a peak of one to three per cent) of derivatized D-amino acids. In every case, the small peak preceding the L-derivative significantly increased in size. We took this peak to be the derivatized D-enantiomer, and calculated enantiomeric excess accordingly. We don't know why the experimental samples showed such varying retention times, while the standards were essentially constant.

(2*S*)-N-(3'-Phenylpropanoyl)bornane-10,2-sultam (2d)- In a 100 mL flask, NaH (1.15 g, Aldrich Chemical Co., 50% in mineral oil, 24.0 mmol) was rinsed with several 10 mL portions of dry toluene (Aldrich Sure/Seal™). A magnetic spin bar was added, the flask was fitted with a septum, and an Ar atmosphere was established. At room temperature, the washed NaH was suspended in 10 mL of dry toluene and a solution of 2.58 g (2*S*)-sultam (12.0 mmol) in 30 mL of dry toluene was added over 5 min *via* a syringe. Some foaming and heating occurred during the addition. After an hour of stirring, dihydrocinnamoyl chloride (1.87 g, 11.0 mmol, Aldrich) was added dropwise over approximately 1 min to the the pale gray slurry. After stirring another hour, the reaction was carefully decomposed with 25 mL of water. Toluene (30 mL) was added and the phases were separated. The organic phase was extracted rapidly with three ice-cold 25-mL portions of 1.0 M NaOH. After drying the toluene solution (Na_2SO_4) and evaporation, 3.49 g (10.0 mmol, 90.9%) of white solid (mp. 151.8-153.0°C; lit. 153-154°) was obtained. The ^{13}C NMR spectrum showed no trace of any material other than the expected product: ($CDCl_3$) 170.61, 139.87, 128.13 (two lines unresolved), 125.90, 64.79, 52.49, 48.09, 47.37, 44.31, 38.12, 36.59, 32.40, 30.14, 26.10, 20.48, 19.53. (The excess sultam was recovered by extracting the acidified base wash with CH_2Cl_2.)

(2*S*,2'*S*)-N-{2'-[^{15}N]Hydroxyamino-3'-phenylpropanoyl}bornane-10,2-sultam (3d)- A mass of 2.43 g (7.00 mmol) of **2d** was placed, along with a spin bar, into a 100 mL flask. After fitting the flask with a septum, an Ar atmosphere was established and 35 mL of dry THF was added. The resulting solution was cooled to -78°C, and

sodium *bis*(trimethylsilyl)amide (7.70 mL of a 1.0 M solution in THF, Aldrich Chemical Co.; 7.70 mmol) was added dropwise with a syringe over 3.5 min. After stirring at -78°C for 70 min, the clear yellow solution was titrated to an olive green end point with a 1.0 M solution of [^{15}N]chloronitrosocyclohexane **6** in THF (7.4 mL; 7.4 mmol)[14]. After stirring 5 min, the reaction was decomposed at -78°C by the addition of 50 mL of 1 M HCl (dropwise at first, then more rapidly). The frozen mixture was allowed to warm to room temperature and evaporated to dryness. The residue was partitioned between 50 mL of 1 M HCl and 100 mL of a 1:1 solution of hexane and diethyl ether. After extracting the ether/hexane with an additional 25 mL of 1 M HCl, the acid portions were combined in a 600 mL beaker, vigorous magnetic stirring was established, and the solution was neutralized to a basic pH with solid sodium bicarbonate. (One must take great care to add the bicarbonate slowly so that the reaction does not foam out of the beaker, especially as the end point of this titration is reached.) The resulting slurry was extracted with three 50 mL portions of CH_2Cl_2. The pooled extract was dried (Na_2SO_4), filtered, and evaporated to give 2.17 g (82% crude yield) of a viscous oil. ^{13}C NMR ($CDCl_3$): 172.29, 136.98, 129.06, 128.10, 126.30, 65.30, 64.97, 52.61, 48.58, 47.52, 44.34, 37.99, 34.43 ($^2J_{C\text{-}N}$ = 2.27 Hz), 32.39, 26.13, 20.49, 19.62. This product was used without further purification.

(2*S*,2'*S*)-N-{2'-[^{15}N]Amino-3'-phenylpropanoyl}bornane-10,2-sultam (4d)- A solution of 2.17 g (5.7 mmol) of crude **3d** in 14.5 mL of glacial HOAc was treated with 29 mL of ice cold 1.0 M HCl. The resulting solution was cooled in an ice bath, and 14.13 g (21.6 mmol) of zinc dust (Aldrich Chemical) was added. This suspension was magnetically stirred in an ice bath for 48 hr in a 3°C cold room. The ice bath was maintained throughout this time. The excess zinc was removed by filtration through a glass wool pad and washed with several portions of glacial HOAc. The combined filtrate was evaporated, leaving behind several grams of a viscous residue. This residue was dissolved in 50 mL of water and extracted with 50 mL of CH_2Cl_2. After two additional 25 mL extractions with CH_2Cl_2, the combined organic phases were washed twice with water, followed by saturated $NaHC0_3$. After drying with Na_2SO_4, filtering, and evaporating, a pale yellow solid (1.95 g, 5.4 mmol crude) remained. The NMR spectrum showed only one product with a small amount of free sultam. ^{13}C NMR ($CDCl_3$): 173.41, 137.47, 129.14, 127.96, 126.09, 64.62, 55.27 ($J_{C\text{-}N}$ = 3.61 Hz), 52.40, 48.32, 47.31, 44.16, 39.21, 37.83, 32.27, 25.94, 20.53, 19.40.

L-[^{15}N]Phenylalanine (5d)- The 1.95 g of **4d** was taken up in 43 mL of THF. The pale yellow, somewhat turbid solution was cooled in an ice bath. Ice cold 1.0 M LiOH (22 mL) was added and this mixture was stirred in an ice bath for 2 hr. After the addition of 21 mL of 1.0 M HCl, the yellow reaction solution was evaporated, leaving a pale yellow solid residue. This residue was partitioned between 50 mL of water and 30 mL of CH_2Cl_2. The colorless aqueous phase was extracted with two additional 30 mL portions of CH_2Cl_2. The organic phases were pooled, dried with Na_2SO_4 and evaporated, leaving 1.17 g of a yellow solid, which was recovered (2*S*)-sultam. The aqueous phase, containing the desired amino acid, was chromatographed as described above. The ninhydrin-positive fraction was evaporated, leaving 0.770 g of white solid (4.63 mmol, 66% from acyl sultam **2d**). ^{13}C NMR (D_2O): 175.01, 136.25, 130.48, 130.24, 128.82, 57.14 ($^1J_{C\text{-}N}$ = 5.76 Hz), 37.45; e.e. = 99.5%.

The other four amino acids listed in the title of this paper were made analogously.

(2*S*)-N-Propanoylbornane-10,2-sultam (2a)- Prepared in 96% yield; mp: 149.4-150.0°C (Lit.[16] 153-154°C) ^{13}C NMR ($CDCl_3$): 172.45, 65.06, 52.72, 48.32, 47.58, 44.49, 38.35, 32.66, 28.71, 26.30, 20.66, 19.72, 8.25.

(2*S*,2'*S*)-N-{2'-[^{15}N]Hydroxyaminopropanoyl}bornane-10,2-sultam (3a)- A mass of 678 mg (2.5 mmol) of propionyl-(2*S*)-sultam was aminated. The product (0.73 g) had ^{13}C NMR ($CDCl_3$): 173.50, 67.38, 59.34, 52.45, 48.37, 47.31, 44.18, 37.77, 32.19, 25.96, 20.60, 19.43, 13.40 ($^2J_{C\text{-}N}$ = 3.50 Hz).

(2*S*,2'*S*)-N-{2'-[^{15}N]Aminopropanoyl}bornane-10,2-sultam (4a)- ^{13}C NMR ($CDCl_3$): 175.28, 64.95, 52.77, 49.62 ($^1J_{C\text{-}N}$ = 3.48 Hz), 48.60, 47.60, 44.39, 38.09, 32.60, 26.22, 20.74, 19.66, 19.03 ($^2J_{C\text{-}N}$ = 2.35 Hz).

L-[^{15}N]Alanine (5a)- After ion chromatography, 115 mg (1.28 mmol) of the amino acid **5a** was obtained. This was a 51% yield based on acylsultam **2a**. ^{13}C NMR (D_2O): 176.88, 51.62 ($^1J_{C\text{-}N}$ = 5.48 Hz), 17.23; e.e. = 97.8%.

(2*S*)-N-{3'-Methylbutanoyl}bornane-10,2-sultam (2b)- Prepared in 91% yield ; mp: 125.0°-126.2° (lit. 129-130°). ^{13}C NMR ($CDCl_3$): 171.48, 65.16. 53.01, 48.21, 47.68, 44.63, 44.18, 38.56, 32.79, 26.41, 25.51, 22.30, 22.24, 20.77, 19.85.

(2*S*,2'*S*)-N-{2'-[^{15}N]Hydroxyamino-3'-methylbutanoyl}bornane-10,2-sultam (3b)- A mass of 748 mg (2.50 mmol) isovaleryl-(2*S*)-sultam (**2b**) was aminated. The product (0.77 g) had ^{13}C NMR ($CDCl_3$): 172.89, 69.29, 64.84, 52.56, 48.21, 47.33, 44.18, 37.85, 32.25, 27.57 ($^2J_{C-N}$ = 1.74 Hz), 25.99, 20.21, 19.88, 19.51, 17.74.

(2*S*,2'*S*)-N-{2'-[^{15}N]Amino-3'-methylbutanoyl}bornane-10,2-sultam (4b)- ^{13}C NMR ($CDCl_3$): 174.36, 64.82, 59.86 ($^1J_{C-N}$ = 2.89 Hz), 52.82, 48.40, 47.52, 44.36, 38.02, 32.57, 30.11, 26.17, 20.74, 19.80, 19.63, 17.73.

L-[^{15}N]Valine (5b)- After ion chromatography, 197 mg (1.66 mmol) of amino acid **5b** was obtained. This was a 66% yield based on acylsultam **2b**. ^{13}C NMR (D_2O): 175.30, 61.46 ($^1J_{C-N}$ = 5.50 Hz), 30.15, 19.04, 17.73; e.e. = 97.8%.

(2*S*)-N-{3'-[1'-^{13}C]Methylbutanoyl}bornane-10,2-sultam- Prepared in 92% yield; mp: 124.8-125.8°C. (lit. 129-130°C) ^{13}C NMR ($CDCl_3$): 170.88, 64.67, 52.50, 47.86 ($^3J_{C-C}$ = 2.64 Hz), 47.29, 44.28, 43.79 ($^1J_{C-C}$ = 49.79 Hz), 38.22, 32.32, 26.06, 25.12 (^2J= 1.85 Hz), 21.99 (^3J = 1.39 Hz), 21.93 (^3J = 1.41 Hz), 20.42, 19.45.

(2*S*,2'*S*)-N-{2'-[1'-^{13}C,^{15}N]Hydroxyamino-3'-methylbutanoyl} bornane-10,2-sultam- A mass of 751 mg (2.50 mmol) of the acyl sultam above was aminated. The product (0.75 g) had ^{13}C NMR ($CDCl_3$): 173.14, 69.56 ($^1J_{C-C}$ = 50.34 Hz), 65.13, 52.85, 48.44, 47.58, 44.36, 38.08, 32.53, 27.81 ($^2J_{C-N}$= 2.40 Hz), 26.20, 20.43, 20.08, 19.74, 17.95.

(2*S*,2'*S*)-N-{2'-[1'-^{13}C,^{15}N]Amino-3'-methylbutanoyl}bornane-10,2-sultam- ^{13}C NMR ($CDCl_3$): 174.32, 64.77, 59.79 ($^1J_{C-C}$ = 51.26 Hz; $^1J_{C-N}$ = 3.50 Hz), 52.77, 48.37 ($^3J_{C-C}$ = 2.48 Hz) 47.49, 44.31, 37.98, 32.52, 30.05, 26.12, 20.69, 19.76, 19.59,17.65.

L-[1-^{13}C,^{15}N]Valine- After chromatography, 211 mg (1.77 mmol) of L-[1-^{13}C, ^{15}N]valine was obtained. This was a 70% yield based on the corresponding acyl sultam. ^{13}C NMR (D_2O): 175.33, 61.46 ($^1J_{C-C}$ = 53.41 Hz; $^1J_{C-N}$ = 5.36 Hz), 30.16, 19.04 ($^3J_{C-C}$ = 2.68 Hz), 17.73; e.e. = 97.2%.

(2*S*)-N-{3'-Methylpentanoyl}bornane-10,2-sultam (2c)- Prepared in 88% yield. This product was initially a viscous colorless oil, which slowly crystallized to a low-melting white solid on standing at room temperature for several days. ^{13}C NMR ($CDCl_3$):

172.03, 65.04, 52.80, 48.21, 47.58, 44.49, 38.37, 33.43, 33.03, 32.66, 27.40, 26.30, 22.15 (equivalent methyl groups), 20.69, 19.74.

(2*S*,2'*S*)-N-{2'-[^{15}N]Hydroxyamino-4'-methylpentanoyl}bornane-10,2-sultam (3c)- A mass of 3.90 g (12.4 mmol) **2c** was aminated. The product (3.26 g) had ^{13}C NMR ($CDCl_3$): 173.35, 65.11, 62.66, 52.83, 48.66, 47.63, 44.41, 38.05, 37.33 ($^2J_{C\text{-}N}$ = 2.43 Hz), 32.53, 26.26, 24.62, 23.12, 21.73, 20.45, 19.73.

(2*S*,2'*S*)-N-{2'-[^{15}N]Amino-4'-methylpentanoyl}bornane-10,2-sultam (4c)- ^{13}C NMR ($CDCl_3$): 172.04, 64.74, 52.41, 51.55 ($^1J_{C\text{-}N}$ = 3.98 Hz), 48.48, 47.37, 44.10, 40.67, 37.66, 32.29, 25.96, 24.02, 22.71, 21.54, 20.35, 19.43.

L-[^{15}N]Leucine (5c)- After ion chromatography, 0.847 g (6.41 mmol) of amino acid **5c** was obtained. This was a 51% yield based on acyl sultam **2c**. ^{13}C NMR (D_2O): 176.62, 54.50 ($^1J_{C\text{-}N}$ = 5.50 Hz), 40.89, 25.25, 23.11, 21.98;e.e. = 98.6%.

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