A Chiral Synthesis of (2*S*,3*S*)-Phenylalanine-3-^{2}H via Boronic Esters

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Summary

Reduction of (s)-pinanediol (*S*)-[(phenyl)(chloro)-methyl]boronate (1) with lithium triethylborodeuteride yielded (s)-pinanediol (*R*)-[(phenyl)methyl]boronate-α-^{2}H (2). The chiral purity of 2 was measured via peroxidic oxidation to (*S*)-benzyl alcohol-α-^{2}H (3), which was analyzed with an NMR chiral shift reagent. (Dichloro-methyl)lithium converted 2 to (s)-pinanediol (1*S*,2*S*)-1-chloro-2-phenylethylboronate-2-^{2}H (4), which with sodium azide yielded (s)-pinanediol (1*R*,2*S*)-1-azido-2-phenylethylboronate-2-^{2}H (5). (Dichloromethyl)lithium with 5 yielded (s)-pinanediol (1*S*,2*S*,3*S*)-1-chloro-2-azido-3-phenylpropylboronate-3-^{2}H (6), which was oxidized by sodium chlorite to (2*S*,3*S*)-2-azido-3-phenylacetic acid-3-^{2}H (7). Hydrogenation of 7 yielded (2*S*,3*S*)-phenylalanine-3-^{2}H (8) in high diastereomeric and enantiomeric purity.

Key words: Phenylalanine, deuterium, boronic ester, chiral label

Introduction

We have recently reported a highly stereoselective general chiral synthesis of amino acids[1] based on our new boronic ester chemistry.[2,3] The new synthesis is particularly well designed for introducing isotopic labels, illustrated here with the highly stereoselective synthesis of chirally labelled L-phenylalanine-3-^{2}H (8).

Chirally labelled L-phenylalanine-3-^{2}H (8) has been prepared previously via an azlactone hydrogenation followed by resolution,[4,5] or from chiral benzyl

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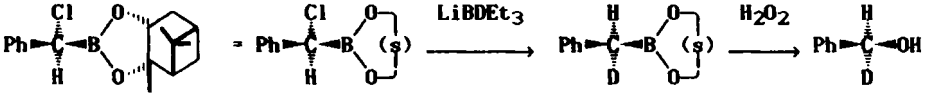
alcohol-α-^{2}H via a standard amino acid synthesis and resolution.[4] The azlactone route is shorter, but 4-10% of the deuterium is lost in making the azlactone. The phenylalanine-3-^{2}H[4] or tyrosine-3-^{2}H[5] was used in studies of enzymatic transformations in plants.

Results

(s)-Pinanediol (1*S*)-1-chloroalkylboronates, which are easily prepared in high diastereomeric purity from (s)-pinanediol alkylboronates and (dichloromethyl)lithium,[2,3] would be expected to yield (1*R*)-alkylboronates-1-^{2}H on reduction with a suitable deuteride source. ["(s)-Pinanediol" refers to "(*S*)-directing" pinanediol from dihydroxylation of (+)-α-pinene.[3]] We tried potassium hydride and observed no reaction, but lithium triethylborohydride readily reduced pinanediol [(phenyl)(chloro)methyl]boronate to the [(phenyl)methyl]boronate. Brown and coworkers have reported that potassium triisopropoxyborohydride reduces 1-chloroalkylboronic esters,[6] and that reagent should also be suitable for introducing deuterium, but in view of the commercial availability of lithium triethylborodeuteride and the ease of its use, we have confined our investigation to this reagent.

Prior to our phenylalanine synthesis, we reduced recrystallized, optically and diastereomerically pure (s)-pinanediol (*S*)-[(phenyl)(chloro)methyl]-boronate[7] (1) to (s)-pinanediol (*R*)-[(phenyl)methyl]boronate-α-^{2}H (2) and oxidized 2 to (*S*)-benzyl alcohol-α-^{2}H (3). The (*R*)-benzyl alcohol-α-^{2}H plus benzyl alcohol-α-^{1}H$_2$ impurity was estimated from the 200 MHz ^{1}H NMR spectrum in the presence of Eu(hfc)$_3$.[8] The impurity level, or perhaps a sideband, was about 2%. It is possible that the ^{1}H content of the reducing agent was this high,[9] though subsequent analysis of the phenylalanine indicated less than 1%. Thus, the reduction appears to be stereospecific.

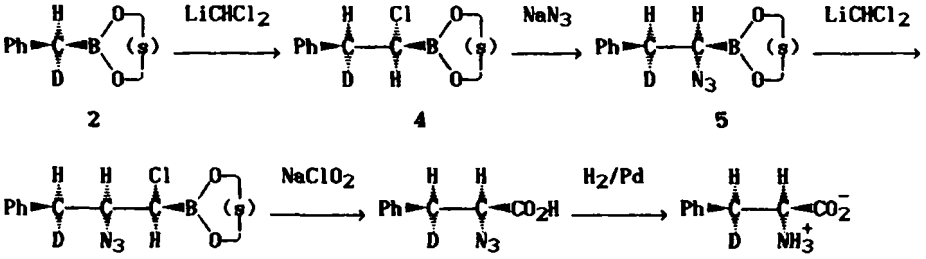


1 2 3

We have also made (s)-pinanediol (*S*)-[(phenyl)(chloro)methyl]boronate-α-^{2}H (1-α-^{2}H) by the simple expedient of using dichloromethane-^{2}H$_2$ as the source of

the (dichloromethyl)lithium-²H, $LiCDCl_2$. However, we have not yet carried out the reduction of this compound with lithium triethylborohydride, which could provide the configuration of chiral deuterium label opposite to that in compounds 2-8.

The conversion of 2 to (2*S*,3*S*)-phenylalanine-3-²H (8) was carried out as outlined. The same chemistry has been reported for the synthesis of unlabelled L-phenylalanine in the preliminary communication.[1]



2 4 5

6 7 8

Evidence for high stereoselectivity of the reaction sequence was provided by 200-MHz NMR spectra. Analyses of intermediates 4 and 5 indicated 3-4% of the wrong diastereomers, consistent with results reported previously for the unlabelled series.[1] The crude (2*S*,3*S*)-phenylalanine-3-²H (8) showed a 5-6% impurity at δ 3.12-3.18, which could include diastereomeric (2*S*,3*R*)- and (2*R*,3*S*)-phenylalanine-3-²H as well as (2*S*)-phenylalanine-3-$^1H_2$. However, the diastereomer appears as a doublet,[4] which could have constituted no more than half of the observed broad absorption, corresponding to 3% diastereomer content. The multiplet characteristic of phenylalanine-3-$^1H_2$ was not visible, though perhaps as much as 0.5-1% could have escaped detection. A single recrystallization removed part of the impurity absorption.

Discussion

Although our synthesis of homochiral benzyl alcohol-α-²H (3) is highly stereoselective and efficient, the reduction of aldehydes with Midland's reagent[10] is generally an easier route to chirally labelled primary alcohols. Our chemistry becomes useful when stereocontrol at adjacent chiral centers is needed.

Our ability to define the chirality error in our synthesis has been limited by our analytical methods. The diastereomeric purity of 1, initially 96-98%,[2,7] is easily increased to 99.5% or better by recrystallization.[7] (Other 1-chloroalkylboronic esters can be made in 99% purity.[3]) It is probable that the displacement of chloride from 1 by deuteride is stereospecific, but our analyses have only proved that the stereoselectivity is at least 98%.

The stereoselectivity of the conversion of [(phenyl)methyl]boronic ester 2 to chloro boronic ester 3 may have been slightly compromised by our use of commercial anhydrous zinc chloride in ether in place of the freshly vacuum dried powdered zinc chloride used previously for this conversion.[3,11] However, the least stereoselective step is probably the displacement of chloride from 3 by azide to form 4, in which 1-2% epimerization has been impossible to avoid.[1,3]

There appears to be no loss of stereochemistry in any of the subsequent steps.[1] Thus, the final crude (2*S*,3*S*)-phenylalanine-3-^2H is contaminated by no more than 2% of the (2*S*,3*R*)-isomer plus L-phenylalanine-3-$^1H_2$, neither of which can be removed. The 3-4% D-phenylalanine is presumably removable by recrystallization, as such levels of enantiomers usually are, and in any event is unlikely to interfere with biochemical applications.

Although we have not carried out the synthesis of the label diastereomer (2*S*,3*R*)-phenylalanine-3-^2H from (s)-pinanediol (*S*)-[(phenyl)(chloro)-methyl]boronate-1-^2H (1-1-^2H), no new chemistry would be required for this operation. The conversion of dichloromethane-$^2H_2$ to (dichloromethyl)lithium-^2H already accomplished was the only step in which it was conceivable that an isotope effect could adversely affect the outcome.

Experimental Section

General Data. Reactions involving carbanions were run under an atmosphere of argon. Tetrahydrofuran (THF) was freshly distilled from benzophenone ketyl. Other reagent grade chemicals were used as purchased. Lithium triethylborodeuteride was "Super Deuteride" purchased from Aldrich Chemical Company.[9] NMR spectra were run on a Nicolet NT-200 or JEOL FX-90 instrument. Chromatography was carried out with Merck 230-400 mesh silica gel.

(*s*)-Pinanediol (*S*)-[(Phenyl)(chloro)methyl]boronate (1). This compound was prepared as described previously[7] and recrystallized from hexane. NMR analysis indicated that the diastereomeric purity was at least 99%; 200 MHz ^{1}H NMR ($CDCl_3$): δ 0.85 (s, 1), 1.14 (d, J=10.8 Hz, 1), 1.30 (s, 3), 1.42 (s, 3), 1.84-2.46 (m, 5), 4.39 (dd, J=2.0, 8.8 Hz, 1), 4.54 (s, 1), 7.25-7.5 (m, 5). Peaks characteristic of the (αR)-epimer were absent [δ 1.03 (d, J=10.7 Hz, 1), 1.28 (s, 3), 1.43 (s, 3), 4.40 (dd, J=1.8, 8.8 Hz)]. (Previously reported NMR data[7] were incomplete and J was erroneous.)

(*s*)-Pinanediol (*S*)-[(Phenyl)(chloro)methyl]boronate (1-α-²H). The preparation of 1 was carried out with dichloromethane-$^2H_2$ in place of dichloromethane-$^1H_2$ to produce (dichloromethyl)lithium-²H. The resulting 1-1-²H had the same 90 MHz ^{1}H NMR spectrum as 1 except that there was no C*H*ClB singlet at δ 4.54.

(*s*)-Pinanediol (*R*)-[(Phenyl)methyl]boronate-1-²H (2). A solution of 1M lithium triethylborodeuteride in diethyl ether (purchased from Aldrich Chemical Company) (4.8 mL, 4.8 mmol) was added dropwise to a solution of 0.98 g (3.22 mmol) of pure 1 in 7 ml of anhydrous tetrahydrofuran stirred under argon at -78 °C. After 15-20 h at 20-25 °C, the mixture was treated with 20 mL of light petroleum and 10 mL of saturated aqueous ammonium chloride. The aqueous phase was washed with 3 X 40 mL of light petroleum and the organic phase was dried over sodium sulfate and concentrated. The crude 2 was chromatographed on silica with 3:1 light petroleum/diethyl ether and concentrated to yield 0.859 g (98%) of 2; 200 MHz ^{1}H NMR ($CDCl)_3$: δ 0.82 (s, 3), 1.05 (d, J=10.8 Hz, 1), 1.27 (s, 3), 1.78-2.38 (m, 5, pinyl CH), 2.32 (t, J=2.2 Hz, 1, PhC*H*D) [lit.[11] $PhCH_2$, 2.35 (s, 2)], 4.27 (dd, J=1.9, 8.7 Hz, 1), 7.05-7.3 (m, 5).

(*S*)-Benzyl Alcohol-α-²H (3). A solution of 2 in a small amount of diethyl ether was stirred with 4 eq of 0.5 M potassium hydroxide in an ice bath and 2 eq of hydrogen peroxide was added in several small portions. After stirring 15-20 h at room temperature the product was extracted with ether. The ether extract was washed with three portions of aqueous potassium borate, until TLC analysis showed that no residual pinanediol remained. Concentration under vacuum yielded a residue of pure benzyl alcohol-α-²H as indicated by the 90 MHz NMR spectrum,

which showed the expected deuterium splitting in the CD*H* absorption at δ 4.56.

Analysis of (*S*)-Benzyl Alcohol-α-^{2}H (3). To a 0.2 M solution of the benzyl alcohol-α-^{2}H in $CDCl_3$ was added 0.7 eq of Eu(hfc)$_3$.[8] With a racemic sample of benzyl alcohol-1-^{2}H, a pair of peaks appeared at δ 11.38 and 11.51. The (*S*)-benzyl alcohol-α-^{2}H showed a strong peak at δ 11.51 and a small peak estimated at 2% at δ 11.39. However, a symmetrically placed bulge of similar magnitude at δ 11.63 suggests that these may be spinning sidebands (25 Hz) rather than the enantiomer or benzyl alcohol-α-$^1H_2$.

(s)-Pinanediol (1*S*,2*S*)-1-Chloro-2-phenylboronate-2-^{2}H (4). A solution of 831 mg (3.06 mmol) of (s)-pinanediol (*R*)-[(phenyl)methyl]boronate (2) in 2 mL of THF was added dropwise to a suspension of 3.68 mmol of (dichloromethyl)lithium in 7 mL of THF at -100 °C, prepared by adding butyllithium to dichloromethane in the manner previously described.[3] A 2.14-mL (2.14 mmol) portion of 1M anhydrous zinc chloride in ether was added and the solution was allowed to warm to room temperature and stirred for 3 h. The mixture was treated with 20 mL of light petroleum followed by saturated ammonium chloride. The aqueous layer was washed with 2 X 30 mL of light petroleum. The combined organic phase was dried over magnesium sulfate, filtered through a plug of magnesium sulfate, and concentrated to yield 980 mg (100%) of 4; 200 MHz NMR ($CDCl_3$): δ 0.83 (s, 3); 1.07 (d, J=10.9 Hz, 1), 1.28 (s, 3), 1.34 (s, 3), 1.75-2.42 (m, 5), 3.19 (d, J=7.6 Hz, 1), 3.65 (d, J=7.6 Hz, 1), 4.35 (dd, J=1.9, 8.7 Hz, 1), 7.26 (m, 5). The ratio of (1*S*)- to (1*R*)-isomer was estimated to be at least 30:1 from the magnitude of the (1*R*)-isomer doublet at δ 0.975. The ratio of (1*S*,2*S*)-isomer to the mixture of (1*R*,2*S*)- and (1*S*,2*R*)-isomer was estimated to be 20-25:1 from the magnitude of the absorptions near δ 3.1.

(s)-Pinanediol (1*R*,2*S*)-1-Azido-2-phenylethylboronate-2-^{2}H (5). A solution of 940 mg (2.94 mmol) of 4 in 30 mL of dichloromethane was added dropwise to a vigorously stirred mixture of 9.6 g (148 mmol) of sodium azide and 60 mg of Aliquat 336 in 65 mL of water and 65 mL of dichloromethane. The mixture was stirred for 40 h.[12] Saturated ammonium chloride was added to aid phase separation. The aqueous phase was extracted with 3 X 40 mL of dichloromethane.

The combined organic phase was dried over sodium sulfate and concentrated. Chromatography on silica with 3:1 light petroleum/diethyl ether yielded 780 mg (81%) of 5; 200 MHz ^{1}H NMR: δ 0.83 (s, 3), 0.97 (d, J=11 Hz, 1), 1.28 (s, 3), 1.37 (s, 3), 1.75-2.45 (m, 5), 2.92 (d, J=8.9 Hz, 1), 3.38 (d, J=9.0 Hz, 1), 4.33 (dd, J=1.8, 8.8 Hz, 1), 7.28 (s, 5). The diastereomeric ratio was estimated to be 20:1 from the δ 3.0 region.

(s)-Pinanediol (1*S*,2*S*,3*S*)-1-Chloro-2-azido-3-phenylpropylboronate-3-²H (6). A solution of 760 mg (2.33 mmol) of 5 in 2 mL of THF was added to 2.8 mmol of (dichloromethyl)lithium[3] in THF at -100 °C. A 3.5-mL (3.5-mmol) portion of 1M anhydrous zinc chloride in ether was added. The solution was allowed to warm to room temperature and stirred overnight, then treated with 20 mL of light petroleum and 20 mL of saturated aqueous ammonium chloride. The aqueous phase was extracted with 3 X 30 mL of light petroleum. The combined organic phase was dried over magnesium sulfate, filtered through a plug of magnesium sulfate, and concentrated to yield 920 mg of crude 6; 200 MHz ^{1}H NMR: δ 0.84 (s, 3); 1.21 (d, J=11.0 Hz, 1), 1.29 (s, 3), 1.42 (s, 3), 1.82-2.47 (m, 5), 2.97 (d, J=7.4 Hz, 1 PhC*H*DCHN$_3$), 3.50 (d, J=4.6 Hz, 1, N$_3$CHC*H*ClB), 3.92 (dd, J=4.6, 7.3 Hz, 1, CHDC*H*N$_3$CHCl), 4.39 (dd, J=1.9, 8.8 Hz, 1), 7.26-7.34 (m, 5).

(2*S*,3*S*)-2-Azido-3-phenylpropanoic Acid-3-²H (7). An 890-mg portion of the crude 6 was dissolved in 40 mL of *t*-butyl alcohol and 13 mL (118 mmol) of 2-methyl-2-butene. A solution of 2.68 g (23.7 mmol) of 80% sodium chlorite and 3.22 g (23.7 mmol) of potassium dihydrogen phosphate in 26 mL of water was added dropwise and the mixture was stirred overnight.[13] The layers were separated and the aqueous phase was washed with 2 X 20 mL of ether. The combined organic phase was concentrated, dissolved in ether, and extracted with three portions of saturated sodium bicarbonate. The aqueous phase was acidified (pH 3) with cold 6M hydrochloric acid and extracted with three portions of ether. The combined organic phase was dried over sodium sulfate and concentrated to yield 370 mg (85% based on 5) of 7; 200 MHz ^{1}H NMR ($CDCl_3$): δ 3.01 (d, J=9.0 Hz, 1, PhC*H*DCHN$_3$) 4.13 (d, J=9.0 Hz, 1, CHDC*H*N$_3$CO$_2$H), 7.25-7.33 (m, 5), 9.0 (broad s, 1, CO$_2$*H*).

(2*S*,3*S*)-Phenylalanine-3-²H (8). A 345-mg (1.79-mmol) portion of the azido

acid (7) in 14 mL of 1:1 ethanol/water was stirred under one atmosphere of hydrogen with 12 mg of platinum oxide for 2 h. Filtration and concentration yielded a white solid which was washed first with ether and then with ethanol to yield 215 mg of crude (2*S*,3*S*)-phenylalanine-3-^{2}H (65% if purity is 90% as estimated from NMR data); recrystallized from water; 200 MHz ^{1}H NMR (D_2O): δ 2.96 (d, J=8.0 Hz, 1, PhC*H*DCH), 3.84 (d, J=7.9 Hz, 1, CHDC*H*(NH_3^+)CO_2^-), 7.15-7.33 (m, 5). From the integral of all of the absorption at δ 3.12-3.18, the ratio of (2*S*,3*S*)-isomer to (2*S*,3*R*)- + (2*R*,3*S*)-isomer was 17:1 before recrystallization, 25:1 afterward. However, the absorption in this region was a bulge with bumps, not the well defined doublet attributable to the diastereomer,[4] and its position was centered 0.02-0.03 δ upfield from where the diastereomer should have been, based on comparison with the spectrum of unlabeled phenylalanine. It appears likely that the diastereomer ratio was at least 30:1 before recrystallization, 50:1 afterward. There was no evidence of any undeuterated phenylalanine in either spectrum at an estimated threshold level of 0.5-1.0%.

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