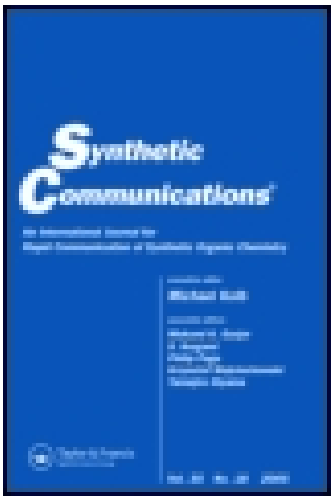

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Synthesis of (R)-(+)-Boc-Iturinic Acid (n-C_{14}) from Aspartic Acid

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SYNTHESIS OF (*R*)-(+)-BOC-ITURINIC ACID (*n*-C_{14}) FROM ASPARTIC ACID

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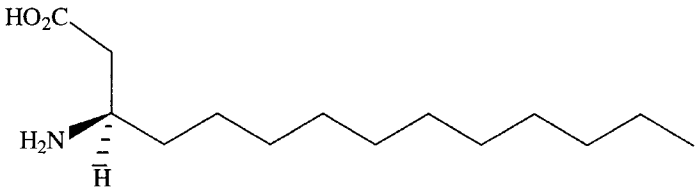
Abstract: The first enantiospecific synthesis of the n-C_{14} isomer of iturinic acid, suitably protected for peptide synthesis, is presented. A new method for the synthesis of enantiomerically pure β-amino acids from aspartic acid is used. The key step consists of an organocuprate addition to a tosylate derivative of aspartic acid, reduced at the α-carboxylic acid.

In recent years the incidence of β-amino acids found in nature, as intermediates in β-lactam syntheses, and as peptide backbone modifications continues to rise. As a result, the synthesis of enantiomerically pure (holemic)[1] β-amino acids has attracted increasing interest.

There have been many methods reported for the asymmetric synthesis of β-amino acids. The need for a synthetic procedure to produce holemic β-amino acids arose in our studies of the structure-activity relationship of the naturally-occurring antifungal peptide, iturin A [cyclo-(Itu-Asn-D-Tyr-D-Asn-Gln-Pro-D-Asn-Ser)],

containing the unusual β-amino acid, iturinic acid (Itu), **1**. This β-amino acid is a common constituent of all peptides in the iturin family that includes the iturins,



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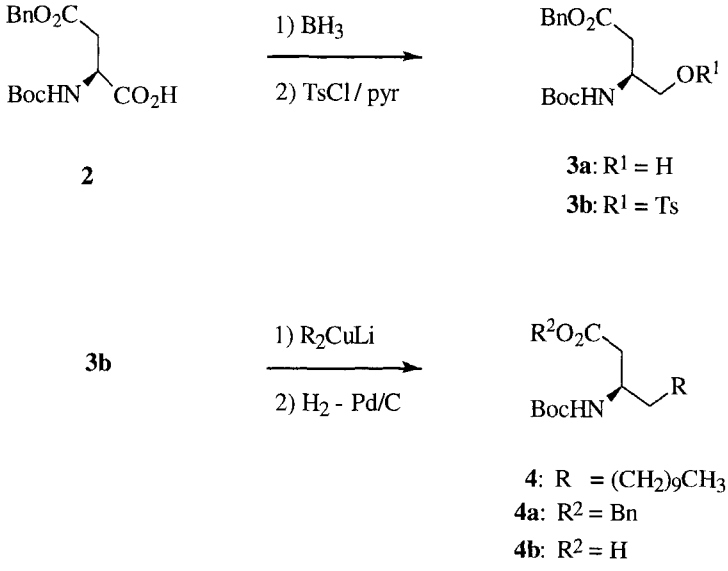
bacillomycins, and mycosubtilin. The iturins contain a mixture of eight isomers of iturinic acid ranging from 13 to 17 carbons in the *normal-*, *iso-*, and *anteiso-* configurations,[2] usually with the predominant isomer having the *n*-C_{14} configuration. It has been determined that iturinic acid has the R-configuration.[3] The synthesis of racemic iturinic acid had been reported, using a multistep procedure, containing as the key step the Wittig reaction of methyl (triphenylphosphoranylidene)acetate with an N-(acetyl)thioamide.[4] We saw the need to improve on this method. Thus, this paper reports an enantiospecific synthesis of the *n*-C_{14} isomer of iturinic acid **4b**, Boc-protected for suitability in peptide synthetic procedures.

From a retrosynthetic perspective, one of the three components (amine, carboxylic acid, and side chain) can be individually coupled to a combination of the other two. Examples of the first two pathways include the Michael addition of lithium amides to an α,β-unsaturated carboxylic esters,[5] and the cycloaddition of nitrones with ketene acetals.[6] These and similar methods obtain stereoselectivity by

Scheme 1



asymmetric induction from the substituents or from a chiral reducing agent, and thus suffer from the production of racemic or scalemic[1] products. Another reported method entails the stereospecific Wolff rearrangement of the diazo-ketone derivative of α-amino acids.[7] This method produces a holemic product but is limited by the lack of unusual side chains available from the natural α-amino acids.

Our approach to the synthesis of holemic β-amino acids (Scheme 1) incorporates the third retrosynthetic pathway of attaching the side chain to the β-amino acid unit. Instead of coupling the side chain directly to the amino-carbon of β-alanine, connection at the γ-carbon of the chiral γ-functionallized-β-amino butyrate **3b** will give a holemic product. Boc-aspartic acid β-benzyl ester, **2**, was utilized as the

starting material for the synthesis of this compound. The β-amino acid unit is already present and both optically active configurations are readily available. This starting material was selectively reduced at the α-carboxylic acid to give the alcohol **3a** in 50% yield by treatment with 1M BH_3·THF at 0°C for 1 h and 4°C overnight. This was an improvement over the failed regiospecific reduction of the dibenzyl methyl ester derivative attempted by Gmeiner,[8b] where reduction at both the α- and β-carboxylates was observed. The alcohol **3a** was converted into its tosylate derivative **3b** in 89% yield by addition of tosyl chloride in pyridine at -20°C, followed by reaction at 0°C for 3h and 4°C overnight. Lithium didecylcuprate was prepared by the addition of 1M decyl lithium / ether (previously prepared from decyl chloride and lithium wire) to purified CuI suspended in ether at -20°C. The reaction was then cooled to -30°C and a solution of tosylate **3b** was added. The solution was allowed to stir for 4.5 h at -30°C, giving **4a** in 86% yield. The β-benzyl ester was then removed by hydrogenolysis with Pd/C to give Boc-Itu **4b** in quantitative yield. Without optimization of conditions, the total yield of **4b** was 38%. Z-Asp β-*t*-butyl ester was also converted into Z-Itu using similar procedures except with a final TFA cleavage of the *t*-butyl ester. The yield of the initial borane reduction was greatly increased (92%) by use of the *t*-butyl ester.

Many of the reported methods for synthesizing β-amino acids have been inapplicable for peptide synthetic procedures because of the protecting groups utilized in their strategies. This procedure affords a Boc-protected amino acid as the product, which can be used directly in peptide synthesis. This method can also provide either desired enantiomer, enantiospecifically.

A similar synthesis from aspartic acid was reportedly[8] attempted, but was unsuccessful. However, the synthesis was successful from the nitrile analog of asparagine. This procedure was considered inadequate because of the multiple steps required for functional group transformations and the requirement of a stringent hydrolysis for final conversion to the β-amino carboxylic acid. This method also employed a dibenzyl protecting group for the amine, which is not conducive to normal peptide synthetic procedures.

A recent publication[9] of independent research has described a similar pathway for the synthesis of β-amino acids, but using the Z-AA-O*t*Bu protection scheme. This method was also used for the synthesis of the fully-protected Z-iturinic acid(*n*-C_{16})-O*t*Bu, a constituent of a minor iturin isomer. Therefore, it was deemed expedient to report on our concurrent research. This paper describes the development of a new synthesis of holemic β-amino acids enabling the first synthesis of (R)-Boc-iturinic acid(*n*-C_{14}), a component of the major isomer of the iturins, suitably protected for peptide synthesis using the common Boc-protection scheme.

Experimental Section

All melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR-200 at 200 and 50.3 MHz, respectively, with TMS as an internal standard. Mass spectra were obtained on a Vestec 201 Electrospray Mass Spectrometer. Optical rotations were measured on an Autopol III Automatic

Polarimeter (Rudolph Research). Elemental analyses were obtained on a Perkin Elmer 2400 CHN Analyzer.

Boc-Asp(OBn)OH was purchased from Sigma Chemical Co. and used without further purification. Borane-tetrahydrofuran complex, *p*-toluenesulfonyl chloride, lithium wire, and 1-chlorodecane were purchased from Aldrich and used without further purification. Tetrahydrofuran was refluxed 24 h and distilled from $LiAlH_4$ prior to use. Ether was dried over sodium pellets.

Thin-layer chromatography was performed on silica gel 60F-254 precoated TLC plates. TLC plates were visualized by using UV light, ninhydrin reagent (0.3% ninhydrin in n-butanol containing 3% HOAc), chlorine-tolidine reagent (1 g of *o*-tolidine dissolved in 100 ml of 10% HOAc, filtered, and mixed 1:1 with 1% KI in H_2O), and/or water spray. The following solvent systems were employed: (I) acetone/petroleum ether (1:2); (II) acetone/petroleum ether (1:4); (III) ethyl acetate/petroleum ether (1:7).

Regular workup implies extraction with 1N $NaHSO_4$ (3 x 1/3 organic volume), 1/2 saturated Na_2CO_3 (3 x 1/3 organic volume), and saturated NaCl (2 x 1/3 organic volume), drying ($MgSO_4$), filtration, and concentration *in vacuo*.

Benzyl 3(S)-[(*tert*-Butoxycarbonylamino)]-4-hydroxy-1-butyrate [Boc-Asp(OBn)-ol] (3a). Boc-Asp(OBn)OH (16.65 g, 51.5 mmol) was dissolved in dry THF (40 ml) and added dropwise *via* syringe, over 45 min, to a 0°C solution of 1M BH_3·THF (103 ml, 103 mmol) under N_2. After stirring 30 min at 0°C, the reaction was stored at 4°C overnight, quenched with 10% HOAc in MeOH (40 ml), and concentrated *in vacuo*. The residue was dissolved in EtOAc (400 ml) and underwent

regular workup to give a yellow oil (10.1 g) which solidified over 3 wks at -20°C. The oily solid was triturated and scraped with petroleum ether (100 ml), filtered, washed with petroleum ether (2 x 50 ml), and dried *in vacuo* to give **3a** as a white solid (7.91 g, 50%): mp 59-62°C; R_f (I) 0.58; $[\alpha]^{25}_D$-3.4° (*c* 1.0 in MeOH); ^{1}H NMR ($CDCl_3$) δ: 7.36 (5H, s, Ph), 5.3 (1H, d, NH), 5.13 (2H, s, CH_2Ph), 4.0 (1H, m, C_βH), 3.7 (2H, d, CH_2-O), 2.65 (2H, d, $C_\alpha H_2$-CO_2R), 1.41 (9H, s, *t*-Bu), 0.9 (1H, m, OH); ^{13}C NMR ($CDCl_3$) δ: 171.6 (Boc-CO), 155.8 (CO-OR), 135.6, 128.6, 128.4, 128.3 (Ph), 79.9 ($C_{t\text{-}Bu}$), 66.7 (CH_2-Ph), 64.4 (CH_2-OH), 49.5 (C_βH), 36.1 ($C_\alpha H_2$), 28.3 ($C_{t\text{-}Bu}H_3$); *m/z* (ES) 332.3 (MNa^+), calcd for $C_{16}H_{23}NO_5$ 309.36. Anal. Calcd for $C_{16}H_{23}NO_5$: C, 62.1; H, 7.5; N, 4.5. Found: C, 62.5; H, 7.6; N, 4.2.

Benzyl 3(S)-[(*tert*-Butoxycarbonylamino)]-4-*p*-toluenesulfonyl-1-butyrate [Boc-Asp(OBn)-CH_2OTs] (3b). A solution of TsCl (11.17 g, 58.6 mmol) in pyridine (50 ml) was added dropwise, over 20 min *via* syringe, to a cooled (-20°C) solution of **3a** (7.25 g, 23.4 mmol) in pyridine (50 ml), under N_2. After stirring 3 h at 0°C, the solution was stored at 4°C for 22 h and then poured into ice-water (1200 ml). The mixture was extracted with ether (3 x 300 ml) and the extracts were combined and subjected to a regular workup (ice cold). After trituration and decanting with petroleum ether (1 x 150 ml, 2 x 50 ml), the product was obtained as a yellow oil (9.68 g, 89%). Purification of 2.60 g by mesh chromatography [140 g mesh silica (15 μ); 70 mm i.d. column; acetone/petroleum ether (1:7) eluant; 1 in/min flow rate; 70 ml/fraction; product adsorbed onto 10 g silica (60-200 mesh)] afforded the product in fractions 19-26. The pure fractions (19-23) were combined and concentrated *in vacuo* to give **3b** as a slightly unstable colorless oil (1.71 g, 66%):

R_f (I) 0.67; R_f (II) 0.32; $[\alpha]^{25}_D$-6.8° (*c* 1.0 in $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 7.77 (2H, d, Ar_{Ts}), 7.36 (7H, d, Ph+Ar_{Ts}), 5.1 (3H, s, NH+CH_2Ph), 4.2, 4.1 (3H, m, $C_\beta H$+CH_2-OTs), 2.65 (2H, d, $C_\alpha H_2$-CO_2R), 2.43 (3H, s, $TsCH_3$), 1.41 (9H, s, *t*-Bu); ^{13}C NMR ($CDCL_3$) δ: 170.5 (Boc-CO), 154.8 (CO-OR), 145.1, 132.5, 130.0, 128.6, 128.4, 128.2, 128.1, 128.0 (Ph+Ar_{Ts}), 79.9 ($C_{t\text{-}Bu}$), 70.2 (CH_2-OTs), 66.7 (CH_2-Ph), 46.4 ($C_\beta H$), 35.3 ($C_\alpha H_2$), 28.3 ($C_{t\text{-}Bu}H_3$), 21.7 ($TsCH_3$); *m/z* (ES) 486.3 (MNa^+), calcd for $C_{23}H_{29}NO_7S$ 463.55.

Benzyl 3(R)-[(*tert*-Butoxycarbonylamino)]-1-tetradecanoate [Boc-Itu$_{nC14}$-OBn] (4a). Decyl lithium was prepared one day in advance as follows: to a three-neck, 100 ml flask, flame dried under dry N_2, was added dry ether (50 ml). Lithium wire (2.13 g, ~45 cm, 0.307 mol) was cut into small pieces in the N_2 stream flowing from the reaction flask. The ether / lithium was refluxed for 1 h, then cooled to 7-10°C. A solution of 1-chlorodecane (22.97 g, 0.130 mmol) in ether (15 ml) was added dropwise over 45 min. After stirring for 1.5 h at 7-10°C, the thick milky suspension was transferred *via* canula, under N_2 pressure, through glass wool to a cooled flask, under N_2. The mixture was stored at -20°C overnight, allowing the unfiltered white solid to settle out of solution. The clear solution was double titrated[10] showing a concentration of 1.09M (67% yield).

The 1.09M decyl lithium (15.91 ml, 17.35 mmol) ethereal solution was added dropwise, *via* syringe over 20 min, to a suspension of purified[11] CuI (1.65 g, 8.67 mmol) in dry ether, cooled to -20°C under N_2, turning from a yellow suspension to a clear brown solution. After stirring another 25 min at -20°C, the reaction was cooled to -30°C and a solution of tosylate **3b** (1.34 g, 2.89 mmol) in dry ether (15 ml)

was added dropwise over 40 min. The mixture was stirred at -30°C for 4.5 h and then quenched with saturated NH_4Cl (12 ml). The brown solution was diluted with ether (230 ml) and EtOAc (50 ml), washed with saturated NaCl (3 x 90 ml) turning the aqueous phase a bright blue. The organic phase was subjected to a regular workup to give a colorless liquid (3.87 g) which solidified at -20°C but melted on returning to r.t. Purification by mesh silica chromatography [140 g mesh silica (15 μ); 70 mm i.d. column; EtOAc/petroleum ether (1:20) eluant; 1 in/min flow rate; 70 ml/fraction; column slurried in petroleum ether and product applied in solution of petroleum ether] afforded the product in fractions 15-30. Fractions 15-30 were combined and concentrated *in vacuo* to give **4a** as a colorless liquid which solidified on cooling to -20°C and remained solid at r.t. (1.08 g, 86%): mp 36.5-37.5°C; R_f (II) 0.65; R_f (III) 0.53; $[\alpha]^{25}_D$+6.6° (*c* 0.5 in MeOH); ^{1}H NMR ($CDCl_3$) δ: 7.35 (5H, s, Ph), 5.1 (2H, s, CH_2Ph), 4.9 (1H, br d, NH), 3.9 (1H, m, $C_\beta H$), 2.55 (2H, d, $C_\alpha H_2$-CO_2R), 1.43 (9H, s, t-Bu_{Boc}), 1.25 (20H, s, $(CH_2)_{10}$), 0.88 (3H, t, CH_3); ^{13}C NMR ($CDCL_3$) δ: 171.5 (Boc-CO), 155.4 (CO-OR), 135.9, 128.6, 128.3 (Ph), 79.2 ($C_{t\text{-}Bu}$), 66.4 (CH_2-Ph), 47.9 ($C_\beta H$), 39.4 ($C_\alpha H_2$), 34.7, ($C_\gamma H_2$), 32.0, ($C_\delta H_2$), 29.66, 29.57, 29.39 ($C_{\epsilon\text{-}\kappa}H_2$), 28.4 ($C_{t\text{-}Bu}H_3$), 26.1 ($C_\lambda H_2$), 22.7 ($C_\mu H_2$), 14.1 ($CH_3$); *m/z* (ES) 456.4 ($MNa^+$), calcd for $C_{26}H_{43}NO_4$ 433.63. Anal. Calcd for $C_{26}H_{43}NO_4$: C, 72.0; H, 10.0; N, 3.2. Found: C, 71.7; H, 10.3; N, 3.0.

3(R)-[(*tert*-Butoxycarbonylamino)]-1-tetradecanoic acid [Boc-Itu$_{nC14}$-OH] (4b). To a solution of benzyl ester **4a** (1.00 g, 2.31 mmol) in MeOH (30 ml), under N_2, was added a catalytic amount of 5% Pd/C. After placing under a H_2 atmosphere, the mixture was stirred overnight at room temperature. The reaction was filtered

through Celite and the solvent was removed *in vacuo* to give **4b** as a white solid (0.79 g, 100%): mp 63-65.5°C; R_f (II) 0.40; $[\alpha]^{25}_D$+5.3° (*c* 1.0 in MeOH); ^{1}H NMR ($CDCl_3$) δ: 7.51 (1H, br s, CO_2H), 4.96 (1H, br d, NH), 3.9 (1H, br s, $C_\beta H$), 2.54 (2H, br s, $C_\alpha H_2$), 1.51 (2H, m, $C\gamma H_2$), 1.44 (9H, s, t-Bu_{Boc}), 1.25 (18H, s, $(CH_2)_9$), 0.88 (3H, t, CH_3); ^{13}C NMR ($CDCL_3$) δ: 176.7 (Boc-CO), 155.7 (CO-OH), 79.5 ($C_{t\text{-}Bu}$), 47.6 ($C_\beta H$), 39.5 ($C_\alpha H_2$), 34.7, ($C_\gamma H_2$), 32.0, ($C_\delta H_2$), 29.66, 29.60, 29.37 ($C_{\epsilon\text{-}\kappa} H_2$), 28.4 ($C_{t\text{-}Bu} H_3$), 26.2 ($C_\lambda H_2$), 22.7 ($C_\mu H_2$), 14.1 ($CH_3$); *m/z* (ES) 366.4 ($MNa^+$), calcd for $C_{19}H_{37}NO_4$ 343.51. Anal. Calcd for $C_{19}H_{37}NO_4$: C, 66.4; H, 10.9; N, 4.1. Found: C, 66.7; H, 10.8; N, 3.8.

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1. These terms are taken from a letter of James H. Brewster to Chemical & Engineering News, 1992, 70(20), 3. Holemic - containing only one enantiomer; scalemic - containing unequal amounts of enantiomers; racemic - containing equal amounts of enantiomers.
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