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TETRAHEDRON: *ASYMMETRY*

A practical stereoselective synthesis of (2*R*,3*S*)-alloisoleucine

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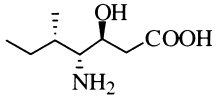
Abstract

An efficient asymmetric Strecker synthesis of the unnatural α-amino acid, D-alloisoleucine (**3**), from commercially available and inexpensive (*S*)-2-methyl-1-butanol (**4**) was accomplished in four steps.

1. Introduction

The didemnins cyclic depsipeptides, isolated from a Carribean tunicate, exhibit antiviral and immunosuppressive properties. Didemnin B was the first congener to enter clinical trials (phases I and II) as a cytotoxic agent.[1–4] The didemnins share a common macrocycle, and differ only in the side chain attachment. The β-hydroxy-γ-amino acid, isostatine (**1**), is a subunit of the didemnin macrocycle and is closely related to statine (**2**) which is found in the protease inhibitor pepstatine.[5,6] Isostatine **1** differs structurally from statine (**2**), having a *sec*-butyl in place of the isobutyl terminus.



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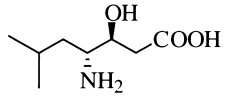

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Rinehart and co-workers reported that **1** is an essential unit for the bioactivity of didemnins.[7,8] An analog in which the isostatine residue (**1**) was replaced with statine (**2**) exhibited lower potency compared with naturally occurring didemnin A. Based on this observation, and that of the spectral data presented by Castro, the identity of **1** versus **2** was confirmed.[9] The structure and configuration of **1** were later obtained by X-ray crystallography.[10]

A convenient approach to **1** utilizes the unnatural α-amino acid, D-alloisoleucine [(2*R*,3*S*)-alloisoleucine] (**3**), which is commercially available, yet expensive.[11] Syntheses of **3** from the more affordable isomer, L-isoleucine [(2*S*,3*S*)-isoleucine], either by inversion of stereochemistry

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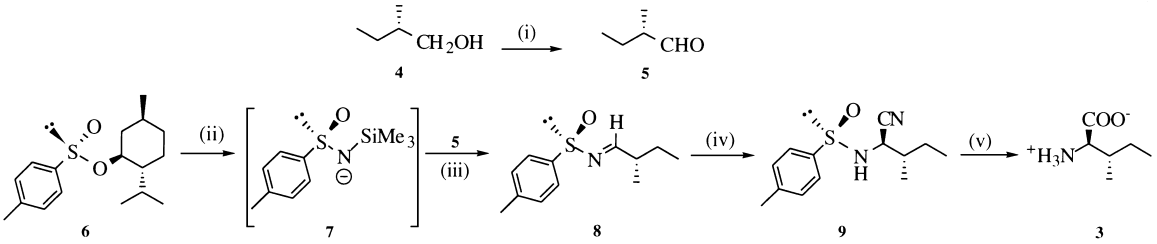
at C-2,[12,13] or by epimerization at the same carbon, followed by enzymatic resolution are rather lengthy.[14] Other approaches include an asymmetric aza-Claisen rearrangement of *N*-2-butenyl-1′-phenylethylcarboximides[15] or S_N2'-alkylation of bromoallenes using organocuprates.[16] Both approaches provided good selectivity. A stereoselective synthesis starting from **4** afforded the protected derivative of **1** in 11 steps.[17]

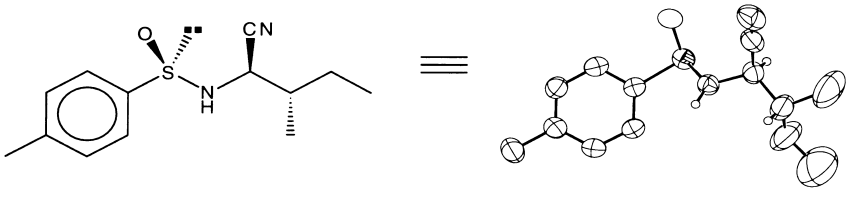
2. Synthesis

We report on an efficient asymmetric Strecker synthesis of **3** from commercially available and affordable (*S*)-2-methyl-1-butanol (**4**) (Scheme 1). This auxiliary controlled synthesis utilizes the enantiopure sulfinimine **8** as a chiral building block. TEMPO-catalyzed oxidation of **4** to the corresponding aldehyde **5**,[18] followed by condensation with the silylsulfinamide anion **7**, gave the enantiomerically pure **8**.[19] The anion **7** was generated in situ by treating (*R*)-(+)-menthyl *p*-toluenesulfinate (Andersen reagent, **6**) with LiHMDS. Imine **8** was used, without further purification, in the next step.



Scheme 1. (i) TEMPO, KBr, NaOCl, CH_2Cl_2 (ii) LiHMDS, −78°C−rt/3 h, THF (iii) **5**, −78°C/1 h, THF (iv) Et(*i*-PrO)AlCN, −78°C−rt/1 h, THF (v) 6 N HCl, reflux

Stereoselective hydrocyanation of **8** using Et(*i*-PrO)AlCN afforded the major α-amino nitrile **9** (de=90%).[20] Recrystallization from a mixture of ether and hexane gave the diastereomerically pure **9**. The stereochemistry of **9** was determined by X-ray crystallography.



Hydrolysis of **9**, under acidic conditions, afforded the enantiomerically pure D-alloisoleucine (**3**) (de=>95%).[21] Compound **3** was transformed to the isostatine unit **1** by sequential activation, β-ketoester formation and reduction.[22] In summary, we have described a highly stereoselective approach to the unnatural α-amino acid, D-alloisoleucine (**3**). The key step in this synthesis is the isolation of the diastereomerically pure α-amino nitrile **9** by recrystallization.

3. Experimental

3.1. General

All solvents were reagent grade and were distilled before use. Diethyl ether and tetrahydrofuran (THF) were distilled from sodium benzophenone. Isopropanol was distilled from calcium hydride and stirred

over 4 Å molecular sieves. Reagent Et_2AlCN was purchased from Aldrich. The Et(*i*-PrO)AlCN complex was formed by treating Et_2AlCN (1.0 equiv.) with *i*-PrOH (1.0 equiv.) in THF at room temperature. Proton magnetic resonance spectra (^1H NMR) and carbon magnetic resonance spectra (^{13}C NMR) were recorded on a Bruker AMX-500 spectrometer operating at 500 MHz and 125.7 MHz, respectively. Chemical shifts are in parts per million (ppm) relative to the solvent as the internal reference. Infrared spectra were obtained on a Perkin–Elmer Model 281-B spectrometer. Absorptions are reported in wavenumber (cm^{-1}). Optical rotations (in degrees) were measured with a Perkin–Elmer Model 241 polarimeter. Elemental analyses were performed on a Perkin–Elmer 2400 Series II CHNS/O analyzer at the University of Pennsylvania. Flash column chromatography was carried out on E. Merck silica gel 60 (240–400 mesh) using the solvent systems listed under the individual experiments.

3.2. (S)-(+)-2-Methylbutanal **5**[18]

Potassium bromide (0.62 g, 5.19 mmol) in water (2 mL) was added dropwise to a solution containing 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) (0.081 g, 0.52 mmol) and (*S*)-(−)-2-methyl-1-butanol (**4**) (4.57 g, 51.9 mmol) in CH_2Cl_2 (100 mL), at 0°C. During the addition, the reaction mixture was stirred vigorously, and the temperature was maintained below 0°C. After 10 min, sodium hypochlorite (156 mL, 156 mmol, 1 M soln) adjusted to pH 9.5 using saturated $NaHCO_3$, was added dropwise to the reaction mixture over a period of 15–20 min. The reaction was allowed to warm to room temperature for an additional 5 min. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3×25 mL). The combined organic layer was washed with 20% HCl (50 mL) containing KI (0.16 g, 1.0 mmol), 10% $Na_2S_2O_3$ (50 mL) and water (50 mL), and dried over Mg_2SO_4. Concentration under reduced pressure provided **5** as a yellow oil, which was used without further purification. ^1H NMR (250 MHz; $CDCl_3$) δ 0.92 (3H, t, *J*=7.2 Hz), 1.06 (3H, d, *J*=7.5 Hz), 1.33 (1H, m), 1.62 (1H, m), 2.2 (1H, m), 9.60 (1H, d, *J*=2Hz); ν_{max} ($CHCl_3$) 2970, 2940, 2890, 2820, 2710, 1725, 1460.

3.3. (R)-(−)-N-[(3S)-Methyl-butylidene]-p-toluenesulfinamide **8**

LiHMDS (24.2 mL, 24.2 mmol, 1 M) was added dropwise to a solution of (*R*)-(+) menthyl *p*-toluenesulfinate (**6**) (5.08 g, 17.3 mmol) in THF (50 mL), cooled to −78°C. After stirring for 10 min, the reaction mixture was warmed to room temperature. After 3.5 h the reaction was again cooled to −78°C and (*S*)-(+)-2-methylbutanal (**5**) was added. The reaction mixture was stirred for 1.5 h and then quenched with saturated NH_4Cl (50 mL). The aqueous layer was extracted with ethyl acetate (2×50 mL). The organic layers were combined, washed with saturated NaCl (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to provide **8** as a yellow oil, which was used in the next step without further purification. R_f 0.5 (ethyl acetate:hexane, 25:75); $[\alpha]_D^{20}$ −343.1 (*c* 7.9; $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.85 (3H, t, *J*=7.0 Hz), 1.1 (3H, d, *J*=7.0 Hz), 1.40 (1H, m), 1.55 (1H, m), 2.40 (1H, s), 2.41 (1H, m), 7.27 (2H, d, *J*=8 Hz), 7.53 (2H, d, *J*=8.2 Hz), 8.09 (1H, d, *J*=5.3 Hz); ^{13}C NMR (500 MHz, $CDCl_3$) δ 11.4, 16.3, 21.4, 26.6, 41.3, 124.6, 129.8, 170.9; ν_{max} ($CHCl_3$) 2963, 2874, 1618, 1096, 1073, 1016. Found C, 64.50; H, 7.7; $C_{12}H_{17}NSO$ requires C, 64.37; H, 7.68%.

3.4. (R)-(−)-[N-p-Tolylsulfinyl]-(2R)-amino-(3S)-methyl-butyronitrile **9**

The Et(*i*-PrO)AlCN complex was cannulated into a solution of **8** dissolved in THF (30 mL), and cooled to −78°C. After 20 min the reaction mixture was slowly warmed to room temperature with stirring. After 40 min the reaction was again cooled to −78°C and quenched with 0.2 N HCl (5 mL).

The reaction mixture was filtered through Celite and the filtrate eluted with EtOAc (80 mL). The organic phase was washed with saturated NaCl (25 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to provide a crude white solid **9**. The solid was crystallized with ether/hexane to afford white crystals (2.3 g, 53%, two steps). R_f 0.5 (ethyl acetate:hexane, 25:75); $[\alpha]_D^{20}$ −55 (*c* 7.6; $CHCl_3$); ^{1}H NMR (500 MHz; $CDCl_3$) δ 0.96 (3H, t, *J*=7.4 Hz); 1.04 (3H, d, *J*=7.0 Hz), 1.21 (1H, m), 1.62 (1H, m), 1.76 (1H, m), 2.40 (1H, s), 4.01 (1H, q, *J*=5.2 Hz) 4.71 (1H, d, *J*=8.0 Hz), 7.34 (2H, d, *J*=8.2 Hz), 7.59 (2H, d, *J*=8.0 Hz); ^{13}C NMR (500 MHz; $CDCl_3$) δ 11.3, 15.4, 21.4, 24.8, 39.2, 47.0, 118.2, 125.8, 129.8, 139.7, 142.4; ν_{max} (KBr) 3238, 3056, 2973, 2876, 1465, 1088, 1064, 1007, 950. Found C, 62.64; H, 7.38; $C_{13}H_{18}N_2SO$ requires C, 62.36; H, 7.19%.

*3.5. (2*R*,3*S*)-Alloisoleucine **3***

Compound **9** (0.43 g, 1.72 mmol) was added to 6 N HCl (4 mL, 24 mmol) and refluxed for 3.5 h. The reaction mixture was then washed with ether (2×10 mL) and the separated aqueous layer was loaded on an ion-exchange resin (Dowex X 50 W X 8-400), eluted with 1.4 N NH_4OH (500 mL) to afford a white solid **3**. (0.22 g, 98%). $[\alpha]_D^{20}$ −17 (*c* 6.4; H_2O), lit.[21] $[\alpha]_D^{25}$ −15.6 (*c* 2.0; H_2O); ^{1}H NMR (500 MHz; D_2O) δ 0.75 (3H, d, *J*=7.0 Hz), 0.85 (3H, t, *J*=7.0 Hz), 1.15 (1H, m), 1.20 (1H, m), 1.70 (1H, m), 3.77 (1H, d, *J*=4.0 Hz); ^{13}C NMR (500 MHz; D_2O) δ 11.4, 13.7, 25.9, 36.0, 58.9, 175.1; ν_{max} (KBr) 3238, 3056, 2973, 2876, 1465, 1088, 1064, 1007, 950.

Acknowledgements

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