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An Organocatalyzed Enantioselective Synthesis of (2*S*,3*R*,4*S*)-4-Hydroxyisoleucine and Its Stereoisomers

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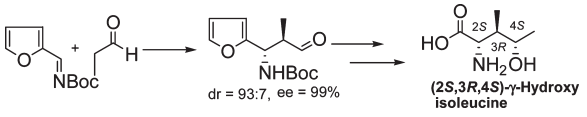

A concise enantioselective total synthesis of (2*S*,3*R*,4*S*)-4-hydroxyisoleucine and its stereoisomers is described. A key feature of this protocol is a catalytic enantioselective mannich reaction that is either *anti*- or *syn*-selective as genesis of chirality.

The nonproteinogenic aminoacid (2*S*,3*R*,4*S*)-4-hydroxyisoleucine **2** has received renewed attention due to its broad range of pharmaceutical activities as insulinotropic, antidyslipidemic, and antihyperglycemic agent.[1] This unusual aminoacid was first isolated as free acid from fenugreek (*Trigonella foenum-graecum*) seeds[2] and the structure was validated by X-ray crystallography,[3] establishing the absolute stereochemistry as 2*S*,3*S*,4*R*. Further, the SAR studies indicated that the absolute configuration of 2*S*,3*R*,4*S* stereogenic centers has considerable influence on their pharmaceutical activity (Figure 1).[4]

In fenugreek (2*R*,3*R*,4*S*)-4-hydroxyisoleucine *ent*-**3** was also found as a minor component. Later on, the (2*S*,3*S*,4*R*)-4-hydroxyisoleucine **3**, which is a component of the natural product funebrine **4**, was isolated from *Quararibea funebris* (Figure 1).[5] Owing to the significant activity of these

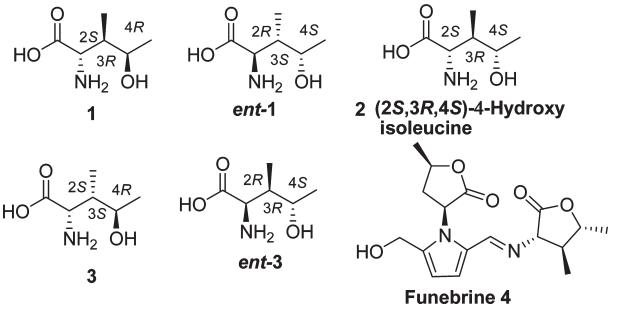

FIGURE 1. Stereoisomers of 4-hydroxyisoleucine.

molecules, impressive synthetic strategies have been reported. To date, most strategies rely on asymmetric induction resulting from either chiral auxiliaries[6] resident chirality or enzymatic kinetic resolution of racemic mixtures.[7]

Herein, we report a highly practical and organocatalyzed enantioselective synthesis of (2*S*,3*R*,4*S*)-4-hydroxyisoleucine and its stereoisomers. In principle, the stereogenic centers 2 and 3 in (2*S*,3*R*,4*S*)-4-hydroxyisoleucine **2** could be accessed through a catalytic enantioselective Mannich reaction that are either *anti*-[8] or *syn*-selective[9] and by using *N*-Boc-furylimine **7** with 1-propanal **8**. We chose furyl moiety as a masked carboxylic acid as well as to enhance its solubility in water.[10] To obtain high selectivities (i.e., de) of the main product, we considered using water as the solvent in the Mannich reaction. Further, the stereogenic center 4 could be realized through a chelation-controlled nucleophilic addition of one carbon Grignard. Additionally, Mitsunobu inversion of stereogenic center 4 in **1**, *ent*-**1**, **3**, and *ent*-**3** would generate a set of four diastereomers. Our retrosynthetic approach is shown in Scheme 1.

Accordingly, readily available furfural derived *N*-Boc-imine **7** was treated with **8** in the presence of a catalytic

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(10) The PMP-protected iminoesters have been used in organocatalyzed Mannich reactions. The protecting group PMP poses potential problems while deprotecting. The Boc-protected iminoesters were not suitable in our case. Hence, *N*-Boc-furylimine was employed in our study, which is easy to prepare and also hydrophilic in nature.

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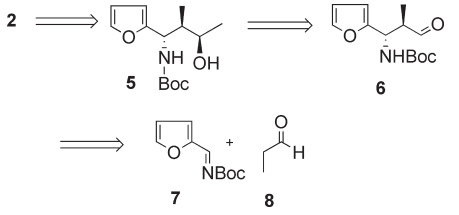
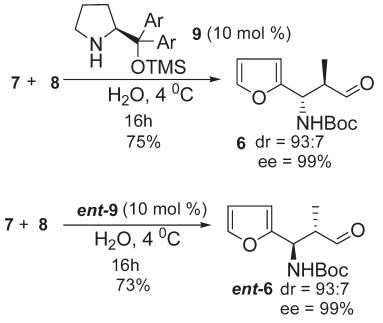
SCHEME 1. Retrosynthesis of (2*S*,3*R*,4*S*)-4-Hydroxyisoleucine



SCHEME 2. TMS-Protected α,α-Diphenyl-2-pyrrolidinemethanol-Catalyzed Synthesis of *β*-Aminoaldehyde



amount of TMS-protected α,α-diphenyl-2-pyrrolidinemethanol **9** (10 mol %) in water at 4 °C for 16 h. The desired *β*-aminoaldehyde **6** was isolated in 75% yield with 93:7 diastereoselectivity and 99% ee (Scheme 2).[8a,11]

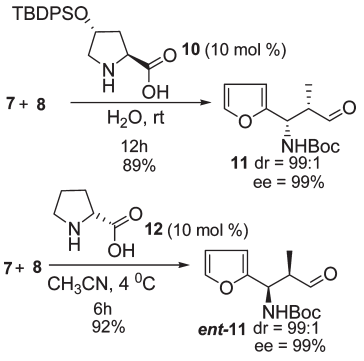
As anticipated, 10 mol % of *ent*-**9** under otherwise identical conditions resulted in *ent*-**6** in 73% yield with the same dr and ee. The diastereoselectivity was determined by integration of one set of ^{1}H NMR signals of the corresponding aldehyde (*δ* major 9.68 ppm as doublet and minor 9.75 ppm as singlet).[11] The ee value was analyzed by HPLC on the chiral staionary phase (Daicel Chiralpak OD-H column: 99/1 *n*-hexane/i-PrOH, flow rate 0.8 mL/min, major = 15.77 min).

In a similar vein, L-proline-catalyzed *syn*-selective Mannich reaction[9a] was evaluated employing **7** and **8** in water. To our surprise, no trace of the desired product **11** was isolated. When a similar reaction was conducted with 10 mol % of 4-*tert*-butyldiphenylsilyloxy L-proline, the required Mannich adduct **11** was isolated in 89% yield with a dr value of 99:1[11] and 99% ee.

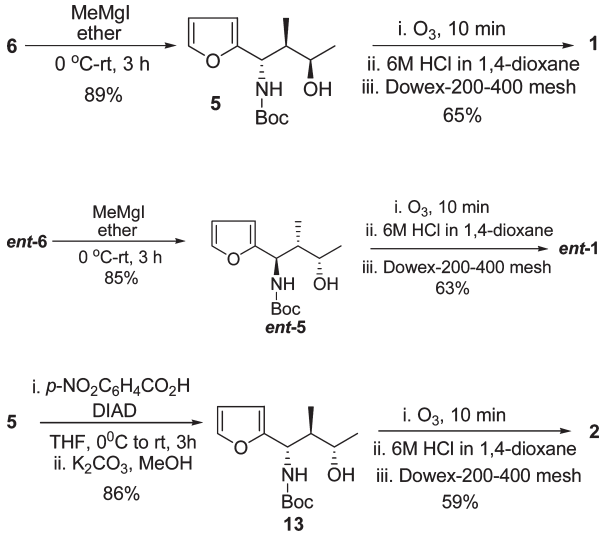
However, the *syn*-variant *ent*-**11** was generated with a catalytic amount of (*R*)-proline **12** (10 mol %) in acetonitrile at 4 °C. The resulting product *ent*-**11** was isolated in good yield (92%) with high diastereo-enantioselectivity (dr 99:1, ee >99%) (Scheme 3).[11] With *anti*−*syn*-varients of *β*-aminoaldehydes in hand, we examined the addition of one carbon Grignard for the synthesis of *β*-aminoalcohols. The exposure of **6** to 1.5 equiv of methylmagnesium iodide at 0 °C to rt for 3 h furnished **5** in 89% yield as the only isolable diastereomer. In the same way, *ent*-**6** subjected to identical conditions (vide infra) resulted in *ent*-**5** in 85% yield with the same optical purity. The diastereoselectivity could be rationalized on the basis of a chelation-controlled mechanism wherein the nucleophile is approaching from the *re-face* of

(11) The dr values of **6**, *ent*-**6**, **11**, and *ent*-**11** have been determined after chromatography of the corresponding reaction mixture (see the Supporting Information).

SCHEME 3. Synthesis of *syn*-Varient *β*-Aminoaldehydes



SCHEME 4. Synthesis of (2*S*,3*R*,4*R*)-4-Hydroxyisoleucine and Its Stereoisomers



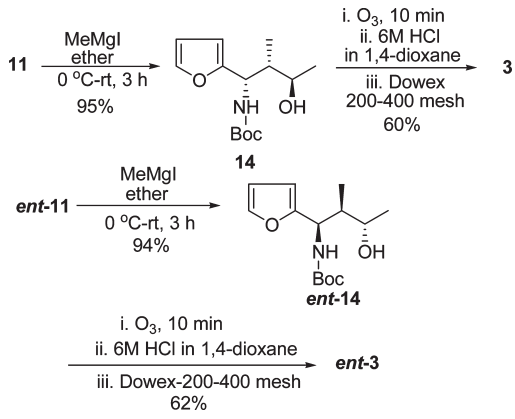
the pro-carbonyl group leading to the observed product **5**, while the adjacent methyl-substituted stereogenic center does not play any significant role.

Oxidative cleavage of the furyl moiety of **5** (O_3, 10 min) followed by Boc deprotection under acidic conditions (6 M HCl in dioxane) and subsequent purification (Dowex 50WX8-400) led to (2*S*,3*R*,4*R*)-4-hydroxyisoleucine **1** in 65% yield. Inversion of stereogenic center 4 in **5** under Mitsunobu conditions (*p*-$NO_2C_6H_4CO_2H$, DIAD, THF, rt, 3 h/K_2CO_3, MeOH) afforded **13** in 86% yield.

Compound **13** was subjected to oxidation, followed by deprotection of the Boc group and purification resulting in the title compound **2** with 59% isolated yield. The chemical data of **2** are identical with those reported for the naturally occurring molecule ($[\alpha]^{24}_D$ +31.2 (*c* 0.9, H_2O), lit.[2] $[\alpha]^{24}_D$ +31 (*c* 1, H_2O)) (Scheme 4). As a result, the absolute stereochemistry of **2** was assigned as 2*S*,3*R*,4*S*, which inturn conformed with the absolute configuration of **1** as 2*S*,3*R*,4*R*.

The above-mentioned addition of Grignard/oxidation/Boc-deprotection was repeated with compound **14** and *ent*-**14** to give **3** and *ent*-**3** in 60% and 62% yields, respectively. The relative stereochemistry of **3** was assigned as 2*S*,3*S*,4*R* based on single X-ray crystallography (CCDC reference no. 764863;[12] the crystal was obtained from 5% EtOAc in hexane (see the Supporting Information)). The optical rotation

SCHEME 5. Synthesis of (2*S*,3*R*,4*R*)-4-Hydroxyisoleucine and Its Stereoisomer



of *ent*-**14** was found to be approximately equal in magnitude to that of **14** but opposite in sign, indicating an enantiomeric relationship, hence stereochemistry of *ent*-**3** was assigned as 2*R*,3*R*,4*S* (Scheme 5).

In conclusion, we have accomplished a concise enantioselective total synthesis of (2*S*,3*R*,4*S*)-4-hydroxyisoleucine **2** and its stereoisomers. Strategic transformation includes a catalytic enantioselective Mannich reaction that is either *syn*- or *anti*-selective as genesis of chirality, methyl Grignard addition, and Mitsunobu inversion to generate eight stereoisomers with perfect stereocontrol. To our knowledge, no catalytic diastereo-enantioselective variant reaction has been explored before for the synthesis of (2*S*,3*R*,4*S*)-4-hydroxyisoleucine. Moreover, flexibility was built into the synthesis to generate a library of analogues. This protocol is also amenable to large-scale synthesis of nonproteinogenic aminoacid.

Experimental Section

***tert*-Butyl (1*S*,2*R*)-1-(Furan-2-yl)-2-methyl-3-oxopropylcarbamate (6).** 1-Propanal **8** (594 mg, 10.25 mmol) and *N*-Boc-protected imine **7** (1.0 g, 5.12 mmol) were added to a round-bottomed flask charged with catalyst **9** (167 mg, 10 mol %) and 2 mL of H_2O at 4 °C. The reaction mixture was stirred for 16 h at this temperature, then the reaction was quenched by addition of EtOAc (15 mL) and the mixture was extracted with EtOAc (3 × 10 mL). The organic layer was separated and dried over Na_2SO_4, concentrated, and evaporated to give crude product. The crude residue was subjected to column chromatography eluting with hexane/EtOAc (95/5) furnishing **6** as a colorless liquid (973 mg, 75%) with dr 93:7 and 99% ee [dr 93:7, determined by integration of one set of ^{1}H NMR signals (δ_{major} 9.65 ppm, d; δ_{minor} 9.73 ppm, s)]. HPLC analysis on a DaicelChiralpak OD-H column: 99/1 *n*-hexane/*i*-PrOH, flow rate 0.8 mL/min, λ = 215 nm; τ_{major} = 15.77 min; $[\alpha]^{24}_D$ +19.8 (*c* 0.9, $CHCl_3$, 99% ee). IR (KBr) 3365, 2979, 2932, 1728, 1681, 1527, 1451, 1372, 1276, 1169, 1051, 919, 753, 612 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.73 (1H, s), 7.34−7.31 (1H, m), 6.30−6.28 (1H, m), 6.20−6.18 (1H, m), 5.21−5.01 (2H, m), 2.97−2.84 (1H, m), 1.44 (9H, s), 1.09 (3H, t, *J* = 7.5 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 202.2, 141.6, 109.8, 106.8, 49.4, 27.7, 9.1; MS (ESIMS) *m*/*z* 254 $(M + H)^+$, 276 $(M + Na)^+$; HRMS (ESI) *m*/*z* 276.1215 (calcd for $C_{13}H_{19}NO_4Na$ 276.1211).

***tert*-Butyl (1*S*,2*R*,3*R*)-1-(Furan-2-yl)-3-hydroxy-2-methylbutylcarbamate (5).** An ether solution of aldehyde **6** (450 mg, 1.78 mmol, 20 mL) was added dropwise to a cooled (0 °C) solution of methylmagnesium iodide prepared from magnesium (64 mg, 2.67 mmol) and methyl iodide (336 mg, 2.67 mmol) in dry ether (15 mL). After addition, the resulting solution was stirred at room temperature for 3 h . The solution was then slowly poured into crushed ice, and the precipitated magnesium hydroxide was quenched by the addition of saturated ammonium chloride (30 mL). The organic layer was separated, and the aqueous phase was saturated with sodium chloride (20 mL) and extracted with chloroform (3 × 15 mL). The combined organic layers were dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure. The crude residue was subjected to column chromatography eluting with hexane/EtOAc (90/10) to furnish **5** as a colorless liquid (425 mg, 89%). $[\alpha]^{24}_D$ +25.8 (*c* 0.9, $CHCl_3$). IR (KBr) 3424, 2278, 2972, 2931, 1675, 1542, 1504, 1365, 1267, 1168, 1092, 1009, 935, 748, 695 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34−7.33 (1H, m), 6.31−6.29 (1H, m), 6.16 (1H, d, *J* = 3.2 Hz), 4.91−4.85 (2H, m), 3.82−3.72 (1H, m), 1.97−1.88 (1H, m), 1.46 (9H, s), 1.21 (3H, d, *J* = 6.2 Hz), 0.95 (3H, t, *J* = 6.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 141.2, 109.9, 106.8, 69.2, 50.3, 45.5, 28.1, 20.2, 11.8; MS (ESIMS) *m*/*z* 270 $(M + H)^+$, 292 $(M + Na)^+$; HRMS (ESI) *m*/*z* 292.1533 (calcd for $C_{14}H_{23}NO_4Na$ 292.1524).

***tert*-Butyl (1*S*,2*R*,3*S*)-1-(Furan-2-yl)-3-hydroxy-2-methylbutylcarbamate (13).** Triphenylphosphine (780 g, 2.98 mmol), *p*-nitrobenzoic acid (279 g, 1.48 mmol), and compound **5** (400 mg, 1.48 mmol) were dissolved in THF (10 mL). To this mixture was added a solution of diisopropylazodicarboxylate (601 mg, 2.97 mmol) in THF (5 mL) at 0 °C via a syring. The reaction contents were stirred at room temperature. After 3 h, the reaction mixture was concentrated under vacuum. The crude residue was dissolved in methanol (20 mL) and cooled to 0 °C. To this was added potassium carbonate (410 mg, 2.97 mmol) portionwise. The mixture was warmed to room temperature over a period of 1 h. Then the solvent was removed under vacuum and the residue was dissolved in CH_2Cl_2 (20 mL). The organic layer was washed with brine (20 mL) and then separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated. The crude residue was subjected to silica gel column chromatography (100−200 mesh), using hexane and ethyl acetate (90:10) as solvents, yielding the pure product **13** as a colorless liquid (344 mg, 86%). $[\alpha]^{24}_D$ +28.8 (*c* 0.9, $CHCl_3$). IR (KBr) 3414, 2281, 2977, 2932, 1678, 1547, 1517, 1366, 1270, 1173, 1092, 1012, 965, 745, 689 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32−7.31 (m, 1H), 6.29−6.31 (m, 1H), 6.19 (1H, m), 5.14−5.12 (1H, m), 4.96−4.84 (1H, m), 3.64−3.62 (1H, m), 1.20−1.98 (1H, m), 1.46 (9H, s), 1.98 (3H, d, *J* = 6.3 Hz), 0.80 (3H, t, *J* = 6.9 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 142.0, 110.7, 106.3, 69.0, 51.9, 43.5, 28.5, 21.1, 8.8; MS (ESIMS) *m*/*z* 270 $(M + H)^+$, 292 $(M + Na)^+$; HRMS (ESI) *m*/*z* 292.1529 (calcd for $C_{14}H_{23}NO_4Na$ 292.1524).

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Supporting Information Available: Experimental procedures and characterization data for all new compounds along with copies of ^{1}H and ^{13}C NMR spectra, and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

(12) The crystallographic coordinates have been deposited with the Cambridge Crystallographic Data Centre; deposition no. 764863. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Rd., Cambridge CB2 1EZ, UK or via www.ccdc.cam.ac.uk/conts/retrieving.html.