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A Practical and Efficient Total Synthesis of Potent Insulinotropic (2*S*,3*R*,4*S*)-4-Hydroxyisoleucine through a Chiral *N*-Protected γ-Keto-α-aminoester

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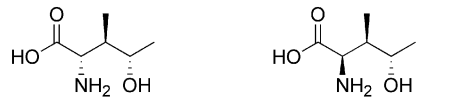
(2*S*,3*R*,4*S*)-4-Hydroxyisoleucine, which exhibits remarkable insulinotropic activity, is expected to be a potent drug to treat type II diabetes. We propose herein a four-step synthesis of the enantiopure natural product on the basis of successive Mannich condensation, catalytic epimerization, *N*-*para*-methoxyphenyl deprotection, and diastereoselective reduction. This compact economical and scalable sequence enables to perfectly control three contiguous chiral centers. It does not involve any chromatographic purification, and the desired compound is obtained in >99 % *de*, >99 % *ee*, and 22 % overall yield under our optimized conditions.

Introduction

Diabetes mellitus is a chronic metabolic disease resulting from insulin deficiency and constitutes an independent risk factor for the development of coronary artery diseases, myocardial infarction, hypertension, and dyslipidaemia.[1] A large number of oral antidiabetic drugs are available today including sulfonylureas, biguanides, thiazolidinediones, α-glucosidase inhibitors, and meglitinides. Although they have been proven effective in controlling hyperglycaemia, they produce troublesome side effects such as hypoglycaemia, nausea, and lactic acidosis. That is why the development of new potent antidiabetic agents has triggered a huge interest in medicinal chemistry.[2]

4-Hydroxyisoleucine (4-OH-iLeu) was first isolated from γ-aminitin hydrolysate and later from ε-aminitin as a new amino acid lactone.[3] Then, Fowden et al. described the isolation and identification of free (2*S*,3*R*,4*R*)-4-OH-iLeu from the seeds of fenugreek, an annual herbaceous plant also called *Trigonella foenum-graecum* Leguminosae.[4]

Much later, the absolute configuration was corrected and confirmed to be (*2S*,*3R*,*4S*) by Alcock et al.[5] In fenugreek natural extract, 4-OH-iLeu exists in two forms as a diastereomeric mixture: major form **1** possesses the (*2S*,*3R*,*4S*) configuration and represents about 90% of the total content and a minor form **2** possesses the (*2R*,*3R*,*4S*) configuration (Figure 1).



major isomer (2*S*,3*R*,4*S*)-4-OH-iLeu (**1**) minor isomer (2*R*,3*R*,4*S*)-4-OH-iLeu (**2**)

Figure 1. 4-OH-iLeu composition of fenugreek seeds.

One major finding is that 4-OH-iLeu acts on both insulin secretion and insulin resistance.[6] Hence, (2*S*,3*R*,4*S*)-4-OH-iLeu (**1**) may be considered as a novel lead. According to the first pharmacological trials, if this natural compound were to be marketed as a potent antidiabetic drug, it would have to be produced on a very large scale (one to six metric tons a day). At present, the only reliable source of **1** is through isolation from fenugreek seeds with an extraction yield of 0.6%. Today, it is obvious that this cumbersome process will not be commercially viable. It appears thus necessary to develop a simple, efficient and economically viable synthesis of **1** from readily available raw materials.

Only few stereoselective syntheses of **1** have been reported. Most approaches are based on the use of biological catalysts.[7] For instance, the sequence elaborated by Potier relies on a microbial diastereo- and enantioselective reduction of ethyl 2-methylacetoacetate by using *Geotrichum candidum* bacteria. The synthesis reported by Martinez et al. is based on final enzymatic resolution by enantioselective hydrolysis of an *N*-phenylacetyl lactone derivative by using immobilized penicillin acylase. Also, the group of Praly published several papers on the synthesis of **1** and its analogues by multistep routes from D-glucose and by ketolization,[8] whereas the group of Martinez published a synthesis based on diastereoselective reduction of chiral dehydroamino acids.[9]

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Results and Discussion

In this paper, we wish to report a novel four-step strategy toward the synthesis of (2*S*,3*R*,4*S*)-4-OH-iLeu (**1**). The first step consists of a proline-mediated Mannich-type condensation followed by a base-promoted epimerization/crystallization to introduce two stereogenic centers and to afford the first optically pure *N*-protected γ-keto-α-aminoester key intermediate **4a**. Then, the third asymmetric center is installed through a one-pot oxidative *N*-deprotection and subsequent diastereoselective reduction. Finally, basic opening of the lactone followed by crystallization yields optically pure **1** with the desired (*2S*,*3R*,*4S*) stereochemistry (Figure 2).

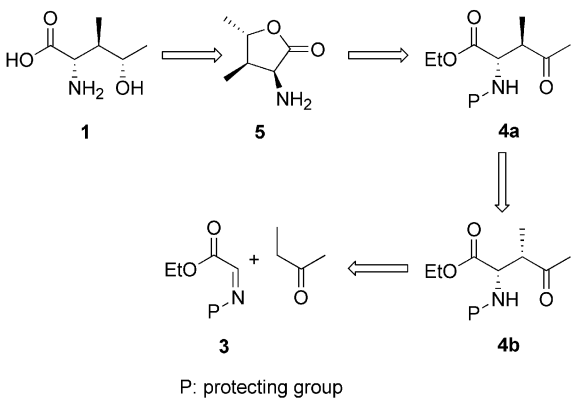
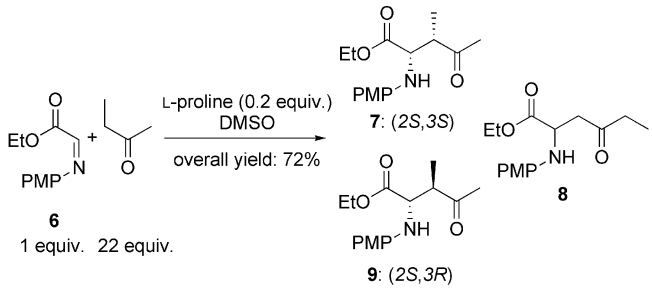


Figure 2. Retrosynthetic analysis for the synthesis of **1**.

During the last few decades, proline-based enamine catalysis has been applied with great success in the synthesis of optically pure amino acids and natural products.[10] Recently, Barbas et al. described an L-proline-catalyzed Mannich-type condensation reaction involving the addition of ketones or aldehydes to *N*-protected α-iminoesters with high enantioselectivities and diastereoselectivities.[11] Such condensation usually affords undesired diastereomer **4b**, which possesses the (*2S*,*3S*) configuration and the wrong configuration at the C3 position. To obtain **4a** with the (*2S*,*3R*) configuration as required to synthesize **1**, several groups have attempted the Mannich condensation by using modified catalysts or the addition of enol silyl ethers to α-iminoesters catalyzed by copper complexes. However in both cases, such catalysts are expensive or harder to access than proline and give lower *ee* values.[12–16]

To overcome that limitation we decided to focus on optimizing the synthesis of undesired **4b** and then to develop conditions to crystallize out the right isomer at C3 under epimerization conditions. The condensation reaction was first performed by using the conditions reported by Barbas with α-iminoesters **3** bearing different protecting groups [P = benzyl, *para*-methoxybenzyl, phenyl, *para*-methoxyphenyl (PMP), allyl, isopropyl, 1-phenylethyl, benzhydryl, hydroxy, methoxy, acetyl, *para*-toluenesulfonyl].

N-PMP-protected α-iminoester **6** was found to give the best overall yield[13] of Mannich addition products (**7** + **8** + **9**). According to the literature, diastereomer **7** resulting from the regioselective nucleophilic attack of the more substituted α carbon atom of 2-butanone should be the sole compound with the (*2S*,*3S*) configuration (>19:1 *dr*, >99% *ee*).[11a] Nevertheless, after the usual workup and purification of the residue by column chromatography, HPLC analysis revealed the presence of a mixture of isomers **7** and **8** in a ratio of 86:14 (Scheme 1). Compound **7** could not be separated from **8** by column chromatography. The overall yield was found to be 72% and separation of **7** from **8** by HPLC was performed to isolate pure **7**. Chiral-phase HPLC analysis confirmed its excellent enantiomeric purity (99%).



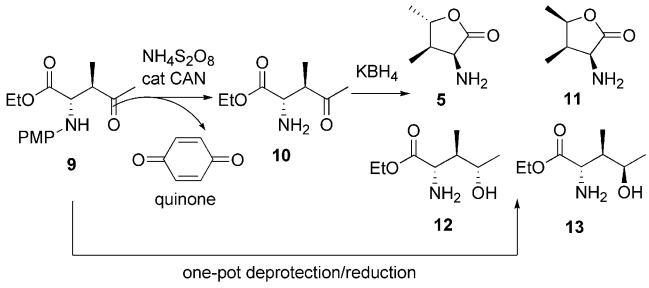
Scheme 1. Proline-catalyzed condensation of iminoester **6** and 2-butanone.

We investigated the influence of solvent in this reaction with a view to optimize the regioselectivity and the recovery of L-proline (see Supporting Information). After 8 h, imine **6** was totally consumed and butanone was evaporated under reduced pressure. When DMF or ionic liquids such as [bmim]Br were used, the L-proline catalyst could be recovered or recycled, respectively.[14] After usual workup, the residue containing **7** and **8** was purified by column chromatography. In the case of [bmim]Br, we observed the formation of only 5% of isomer **8** (11% with DMF). However, the ionic liquid requires vigorous mixing for a good solubilization of the starting materials at room temperature. The choice of solvent will depend on the ability to purge isomer **8** after the epimerization step.

To afford the desired (*2S*,*3R*) configuration, Mannich product **7** (+ **8**) was submitted to epimerization by action of a catalytic amount of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN, 0.04 equiv.) in methyl *tert*-butyl ether (MTBE). After complete air evaporation of MTBE, the resulting solid containing (*2S*,*3R*) diastereomer **9** and isomer **8** (only trace amounts of **7**) was crystallized from ethyl alcohol to give pure desired diastereomer **9** as a solid with >99% *ee* and >99% *de*. Most interestingly, this epimerization step can be performed directly on the crude Mannich condensation mixture without any intermediate purification. This is advantageous, as it permits to conveniently remove isomer **8** by the simple process of recrystallization.

Furthermore, using DMF as the solvent in the first step allows 70% recovery of L-proline by simple filtration. To sum up, this first sequence Mannich reaction in DMF followed by isomerization afforded crystalline *N*-protected γ-keto-α-aminoester **9** bearing two of the three required stereocenters with an overall yield of 50% without any chromatographic purification.

The second part involving PMP deprotection and reduction of the γ ketone can be performed in two ways: deprotection/reduction or reduction/deprotection (see the Supporting Information). We investigated both alternatives and found that the most effective was to carry out first the PMP cleavage and then the ketone reduction (Scheme 2).



Scheme 2. One pot deprotection and reduction of **9**.

The most widely used oxidant to perform PMP deprotection is ceric ammonium nitrate (CAN).[15] However, we evaluated deprotection with the nontoxic and cheap ammonium persulfate oxidant to obtain an economical and environmentally friendly process.[16] Only a few successful PMP cleavages using this oxidant have been described in the literature.[17] In our case, two equivalents of ammonium persulfate were required at 35 °C in acetonitrile and water to drive the deprotection to completion. Desired γ-keto-α-aminoester **10** was obtained in 70% yield (compared to 85% with CAN). Addition of a catalytic amount of CAN (0.1 equiv.) to $(NH_4)_2S_2O_8$ resulted in an improved yield of 82%. It should be mentioned that epimerization at C3 after isolation of **10** occurs if the compound is not used quickly in the next step of reduction.

Using the aforementioned crude deprotection mixture, various reaction conditions were tested for the reduction of **10**. Reduction of **10** was carried out with potassium borohydride KBH_4 (1.5 equiv.) and other hydrides in MeOH in the presence or absence of a chelating reagent such as $CeCl_3$, $LaCl_3$, $SmCl_3$, or $GdCl_3$. After usual workup, the crude mixture was directly analyzed by ^1H NMR spectroscopy to determine the diastereoselective ratio. When the reaction was carried out in the presence of a chelating reagent, the resulting mixture was composed of **5** and **11** and open forms **12** and **13**. Therefore, the *dr* was determined on the mixture of 4-OH-iLeu after hydrolysis of the aminolactones and opened forms.

Representative results using KBH_4 and $CeCl_3$ depending on the temperature are summarized in Table 1. Other results are described in the Supporting Information

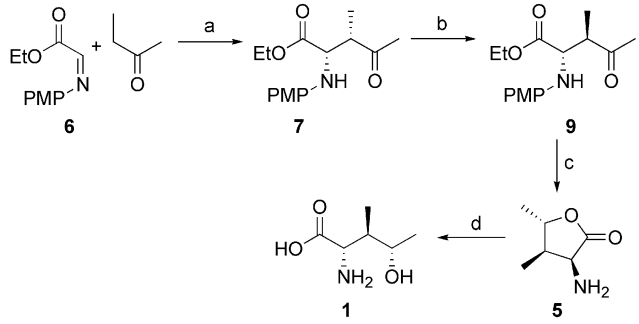
At 0 °C in the presence of $CeCl_3{\cdot}7H_2O$ (0.4 equiv.) aminolactones **5** (+ **12**) and **11** (+ **13**) were obtained in a 70% overall yield and an 80:20 ratio (Table 1, Entry 2). The selectivity was dramatically decreased when the reaction was carried out at ambient temperature (Table 1, Entry 3) and slightly improved when the reaction was performed at –10 °C (Table 1, Entry 1). Interestingly, the use of KBH_4 in the absence of cerium(III) resulted in reversed diastereoselectivity, affording aminolactones **5** and **11** in 82% overall yield with a 25:75 ratio at 0 °C (Table 1, Entry 4) and in 80% overall yield and a 10:90 ratio at room temperature (Table 1, Entry 5).

Table 1. Reaction conditions for the diastereoselective reduction of **10**.

Entry	Additive (0.4 equiv.)	*T* [°C]	Diastereomers **5** + **12**	**11** + **13**	Yield [%]
1	$CeCl_3{\cdot}7H_2O$	–10	85	15	70
2	$CeCl_3{\cdot}7H_2O$	0	80	20	70
3	$CeCl_3{\cdot}7H_2O$	20	55	45	72
4	–	0	25	75	82
5	–	20	10	90	80

To further improve the procedure and to avoid the isolation of intermediate **10**, we envisaged a one-pot procedure for the PMP deprotection and reduction steps. Once deprotection of **9** with $(NH_4)_2S_2O_8$ and a catalytic amount of CAN was completed as evidenced by TLC analysis, the quinone side product was eliminated by washing the reaction mixture with dichloromethane. Then, the resulting aqueous layer containing **10** was neutralized with a 2 N sodium carbonate aqueous solution at 0 °C, and treated with $CeCl_3{\cdot}7H_2O$ (0.4 equiv.) followed by KBH_4 (1.5 equiv.) at –10 °C. The temperature was allowed to increase progressively to 10 °C. After pH adjustment of the mixture to 9 and several extractions with dichloromethane, lactones **5** (+ **12**) and **11** (+ **13**) were afforded in an 80:20 ratio (70% yield).

The mixture was then subjected to hydrolysis by treatment with aqueous LiOH.[7b] When the reaction was completed as evidenced by TLC analysis (2 h), acetic acid was added until the pH of the reaction mixture reached 5. Water was removed under reduced pressure, and the residue was recrystallized from 95% EtOH to provide a first batch of optically pure (2*S*,3*R*,4*S*)-4-OH-iLeu (**1**) as a single enantiomer and diastereomer. The mother liquor, containing (2*S*,3*R*,4*S*)-4-OH-iLeu (**1**) and (2*S*,3*R*,4*R*)-4-OH-iLeu, was



Scheme 3. Overall synthetic scheme for the synthesis of **1**. Reagents and conditions: (a) i. DMF, L-proline (0.35 equiv.), room temp., 8 h; ii. filtration; iii. hickmann; (b) i. MTBE, DBN (0.04 equiv.), room temp., 24 h; ii. crystallization in EtOH, >99% *de*, >99% *ee*, 50% yield from *p*-anisidine; (c) i. $(NH_4)_2S_2O_8$ (2 equiv.), CAN (0.1 equiv.), 0–35 °C, 3 h; ii. 2 N Na_2CO_3; iii. $CeCl_3{\cdot}7H_2O$ (0.4 equiv.), KBH_4 (1.5 equiv.), –10 °C to 10 °C, 1.5 h, *dr* = 80:20, 70% yield; (d) i. LiOH (1.5 equiv.), H_2O; ii. AcOH; iii. recrystallization in EtOH and mother liquor passed through a column of Dowex 50WX8–200 column ion-exchange resin, 65% overall yield.

passed through a column of ion-exchange resin and recrystallized from 95% EtOH to provide the second batch of enantiopure **1** (65% overall yield from the aminolactone mixture).

To sum up, enantiomerically pure (2*S*,3*R*,4*S*)-4-OH-iLeu (**1**) was obtained in good overall yield (22%) from cheap,[17] commercially available raw materials (Scheme 3). The straightforward strategy involves only standard solvents and reaction conditions excluding cryogenic steps, and simple isolations and material purity upgrades allowed us to obtain (2*S*,3*R*,4*S*)-4-OH-iLeu (**1**) in >99%*de* and >99%*ee*.

Conclusions

Our synthetic route is amenable and has been carried out on a 50-g scale and further scaling up appears feasible without major difficulties.[18] Moreover, the synthesis can be easily adapted to the synthesis of all other stereoisomers of 4-OH-iLeu as well as to the synthesis of structurally related analogues by adjusting the reaction sequence and catalyst stereochemistry. That work is currently in progress and will be reported in due course.

Experimental Section

Ethyl (2*S*,3*S*)-2-(4-Methoxyphenylamino)-3-methyl-4-oxopentanoate (7): 2-Butanone (761 mL, 22 equiv.), dry DMF (600 mL), and L-proline (15.5 g, 0.35 equiv.) were mixed and stirred at room temperature under an atmosphere of nitrogen. Imine **6** (386 mmol) dissolved in dry DMF (200 mL) was added slowly, and the resulting mixture was stirred at room temperature for 8 h. After ensuring the absence of imine by TLC, L-proline was removed by filtration (12 g recovered) and butanone and DMF were removed under reduced pressure. Mannich condensation product **7** was directly used without purification for the next step of epimerization. However, it can be purified by flash chromatography on silica gel (hexane/EtOAc, 85:15) to give 72% of a yellow oil (278 mmol, 77.5 g) containing **7** and its regioisomer **8**. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21 (t, J = 7.1 Hz, 3 H, $CHCOOCH_2CH_3$), 1.23 [d, J = 7.3 Hz, 3 H, $CH(CH_3)COCH_3$], 2.21 [s, 3 H, $CH(CH_3)COCH_3$], 3.01 [m, 1 H, $CH(CH_3)COCH_3$], 3.72 (s, 3 H, OCH_3), 3.90 (br. s, 1 H, *NH*), 4.15 (q, J = 7.1 Hz, 2 H, $CHCOOCH_2CH_3$), 4.31 (d, J = 5.6 Hz, 1 H, $CHCOOCH_2CH_3$), 6.62–6.66 (d, J = 9.1 Hz, 2 H, *Ph*), 6.74–6.78 (d, J = 9.1 Hz, 2 H, *Ph*) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 12.2, 14.1, 28.5, 49.2, 55.6, 59.5, 61.3, 114.8, 115.7, 140.8, 153.1, 172.8, 209.2 ppm. IR: $\tilde{\nu}$ = 3365, 2981, 1726, 1713, 1512, 1235, 1180, 1033, 823 cm^{-1}. $[a]_D^{20}$ = –37.9 (c = 1, CH_2Cl_2) {ref.[11c] $[a]_D^{20}$ = –71.3 (c = 1, $CHCl_3$)}. TLC: R_f = 0.18 (cyclohexane/EtOAc, 80:20). MS (CI): m/z = 280 [M + H]$^+$. HRMS: calcd. for $[C_{15}H_{21}N_1O_4H]^+$ 280.1543; found 280.1530. GC–MS t_R = 17.33 min. HPLC (hexane/ethanol, 99:1; 6 mL min^{-1}): t_R = 10.70 min.

Ethyl (2*S*,3*R*)-2-(4-Methoxyphenylamino)-3-methyl-4-oxopentanoate (9): To the crude reaction mixture (approximately 278 mmol) dissolved in MTBE (15 mL) was added DBN (1.4 mL, 11.1 mmol, 0.04 equiv.). The reaction was stirred under an atmosphere of nitrogen flux for 2 h. The MTBE was evaporated slowly overnight at room temperature. A solid cake was obtained and was dissolved in hot 95% EtOH to give by crystallization compound **9** (54 g, 194 mmol) as a white solid (overall yield from *p*-anisidine: 50%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21 [m, 6 H, $CHCOOCH_2CH_3$, $CH(CH_3)COCH_3$], 2.24 [s, 3 H, $CH(CH_3)COCH_3$], 3.03 [m, 1 H, $CH(CH_3)COCH_3$], 3.75 (s, 3 H, OCH_3), 4.17 (m, 4 H, *NH*, $CHCOOCH_2CH_3$, $CHCOOCH_2CH_3$), 6.65–6.68 (d, J = 9.0 Hz, 2 H, *Ph*), 6.76–6.79 (d, J = 9.0 Hz, 2 H, *Ph*) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 12.8, 14.0, 28.5, 49.2, 55.5, 60.3, 61.1, 114.7, 115.6, 140.6, 152.9, 172.4, 209.4 ppm. IR: $\tilde{\nu}$ = 3337, 2975, 1731, 1701, 1515, 1234, 1160, 1035, 816 cm^{-1}. $[a]_D$ = –32.3 (c = 1, CH_2Cl_2). TLC: R_f = 0.18 (cyclohexane/EtOAc, 80:20). MS (CI): m/z = 280 [M + H]$^+$. HRMS: calcd. for $[C_{15}H_{21}N_1O_4H]^+$ 280.1543; found 280.1533. HPLC (hexane/ethanol, 99:1; 6 mL min^{-1}): t_R = 9.95 min. GC–MS t_R = 17.27 min. M.p. 98.8–99.3 °C.

(3*S*,4*R*,5*S*)-3-Amino-4,5-dimethyldihydrofuran-2(3*H*)-one (5): Compound **9** (11.6 g, 41.6 mmol) was dissolved in acetonitrile (20 mL), and the mixture was stirred at 0 °C. A solution of $(NH_4)_2S_2O_8$ (19 g, 83.2 mmol, 2 equiv.) and CAN (2.3 g, 4.16 mmol, 0.1 equiv.) in H_2O (120 mL) was added at 0 °C, and the reaction mixture was heated to 35 °C for 3 h. The reaction mixture was extracted with CH_2Cl_2 (4 × 150 mL) to purge the quinone, and the aqueous phase containing **10** was neutralized to pH 7 at 0 °C with 2 N Na_2CO_3. The reaction flask was cooled to –10 °C under vigorous stirring. $CeCl_3 \cdot 7H_2O$ (6.2 g, 16.6 mmol, 0.4 equiv.) was added, and the mixture was stirred vigorously for 10 min. Then, KBH_4 (3.4 g, 62.4 mmol, 1.5 equiv.) was added carefully in 3–4 portions over a 10 min period. The reaction mixture was warmed up to 10 °C for 1.5 h until TLC indicated the absence of the starting material. The reaction mixture was basified at 0 °C with 2 N Na_2CO_3 to adjust to pH 9 and extracted with CH_2Cl_2 (5 × 400 mL). The combined organic phase was washed with H_2O, dried with Na_2SO_4, and evaporated under reduced pressure to give the lactone mixture (3.75 g, 29.1 mmol) in 70% yield. Data for **5**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.09 [d, J = 7.1 Hz, 3 H, $CH(CH_3)CHNH_2$], 1.40 [d, J = 6.5 Hz, 3 H, $COOCH(CH_3)$], 2.29 [m, 1 H, $CH(CH_3)CHNH_2$], 3.80 [d, J = 7.3 Hz, 1 H, $CH(CH_3)CHNH_2$], 4.32 [m, 1 H, $COOCH(CH_3)$] ppm. MS (CI): m/z = 130 [M + H]$^+$. GC–MS t_R = 6.37 min. Data for **11**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.91 [d, J = 7.1 Hz, 3 H, $CH(CH_3)CHNH_2$], 1.36 [d, J = 6.8 Hz, 3 H, $COOCH(CH_3)$], 2.57 [m, 1 H, $CH(CH_3)CHNH_2$], 3.85 [d, J = 7.2 Hz, 1 H, $CH(CH_3)CHNH_2$], 4.56 [m, 1 H, $COOCH(CH_3)$] ppm. MS (CI): m/z = 130 [M + H]$^+$. GC–MS t_R = 6.85 min.

(2*S*,3*R*,4*S*)-2-Amino-4-hydroxy-3-methylpentanoic Acid (1): To the lactone mixture (29.1 mmol) dissolved in H_2O (0.3 M, 96 mL) was added LiOH (1.05 g, 43.6 mmol, 1.5 equiv.), and the reaction mixture was stirred at room temperature for 2 h. After ensuring completion checked by TLC, the reaction mixture was carefully acidified with AcOH to pH 5. H_2O was completely removed by successive azeotropic distillations with EtOH. The solid obtained was recrystallized from 95% ethanol to give **1** (2.3 g), and the mother liquor was passed through a column of Dowex 50WX8–200 ion-exchange resin (H+ form) and recrystallized from 95% ethanol to give an additional amount of **1** (0.5 g). Overall, **1** (2.8 g, 18.9 mmol) was obtained 98% pure with an overall yield of 65%. ^{1}H NMR (200 MHz, D_2O): δ = 0.95 [d, J = 6.6 Hz, 3 H, $CH(CH_3)CH(OH)CH_3$], 1.23 [d, J = 5.6 Hz, 3 H, $CH(CH_3)CH(OH)CH_3$], 1.91 [m, 1 H, $CH(CH_3)CH(OH)CH_3$], 3.84 [m, 1 H, $CH(CH_3)CH(OH)CH_3$], 3.90 (m, 1 H, *CH*COOH) ppm. ^{13}C NMR (75 MHz, D_2O): δ = 12.7, 21.3, 41.9, 57.5, 70.5, 174.3 ppm. IR: $\tilde{\nu}$ = 3045, 2964, 1625, 1454, 1310, 1101, 815 cm^{-1}. $[a]_D^{20}$ = +30.7 (c = 1, H_2O) {ref.[7b] $[a]_D^{20}$ = +31 (c = 1, H_2O)}. M.p. 215–222 °C {ref.[7b] m.p. 224 °C}. HRMS: calcd. for $[C_6H_{13}N_1O_3H]^+$ 148.0968; found 148.0974.

Supporting Information (see footnote on the first page of this article): Experimental and analytical procedures.

Acknowledgments

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