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A practical synthesis of enantiopure β-methyltryptophan ethyl ester for a preparation of diabetes drug

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ABSTRACT

A practical synthesis of (2*R*,3*S*)- and (2*S*,3*R*)-β-methyltryptophan ethyl ester (β-MeTrp-OEt) has been developed. Racemic *threo*-β-MeTrp-OEt was diastereoselectively prepared via crystallization-induced diastereomer transformation (CIDT) of the α-nitro equivalent of β-MeTrp-OEt. The enantiomers were resolved via diastereomeric salt formation using a half equivalent of (*R*)-2-(4-hydroxyphenoxy)propionic acid. The process allowed a diabetes drug candidate *N*-[(1*R*,2*S*)-1-({5-[(dimethylamino)methyl]-2-ethoxyphenyl}aminocarbonyl)-2-(1*H*-indol-3-yl)propyl]-4-phenyl-1-piperidinecarboxamide to be prepared in good yield with high quality.

1. Introduction

Incorporating appropriate conformationally constrained amino acids into biologically active compounds is a well-known approach to increase their receptor selectivity and to modulate their efficacy.[1–3] In this context, β-methyltryptophan (β-MeTrp) has received considerable attention in the field of peptide-based drug design,[4–7] and it has been used as a bioisostere of amino acid residue of peptide mimetic compounds (Fig. 1), such as the diabetes drug candidates *N*-[(1*R*,2*S*)-1-({5-[(dimethylamino)methyl]-2-ethoxyphenyl}aminocarbonyl)-2-(1*H*-indol-3-yl)propyl]-4-phenyl-1-piperidinecarboxamide (**1**),[8] L-054,522,[9] and L-779,976.[10]

Since the pioneering work of Snyder,[11] a large number of attempts at the synthesis of β-MeTrp have been undertaken.[12,13] For example, optically active β-MeTrp has been prepared by classical resolution via diastereomeric salt formation[14,15] and by kinetic resolution using enzymatic hydrolysis.[16] Although enantioselective syntheses of β-MeTrp were also reported,[17–20] from the viewpoint of large-scale production, these methods have significant drawbacks, such as the requirement of long synthetic steps, manipulation of expensive chiral auxiliaries, and usage of multiple protective groups.

As for the large-scale preparation of unnatural α-amino acids with a wide variety of side chains, a catalytic asymmetric hydrogenation based-process may be considerable as an attractive method. Indeed, the asymmetric hydrogenation of readily preparable α-hydroxycarbonyl- or α-alkoxycarbonyl-substituted enamides has frequently been applied to their preparations since the successful application of L-Dopa.[21] However, the method has not generally been applied to the preparation of β-branched-α-amino acids that require simultaneous chirality control of the adjacent asymmetric centers, because the preparation of β,β-disubstituted α-enamide precursors

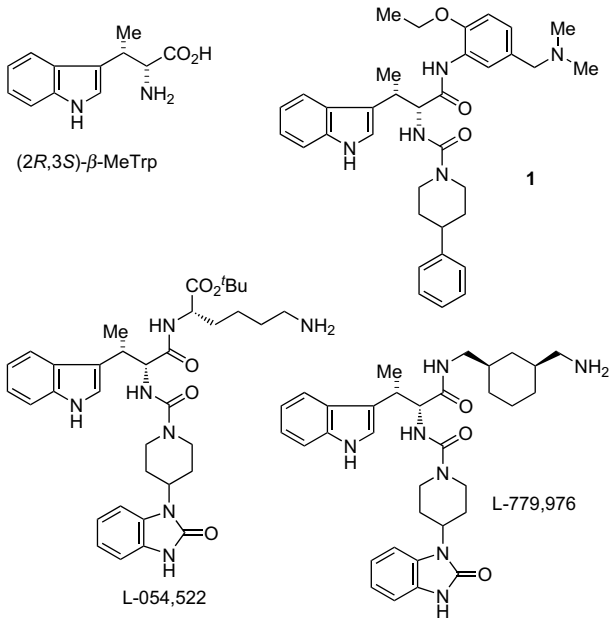

Figure 1. β-MeTrp and diabetes drug candidates incorporating the β-MeTrp structure.

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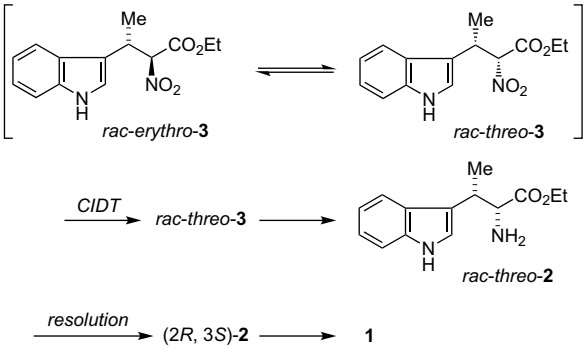
involves additional issues of geometric selectivity.[22] In the case of β-MeTrp, the chromatographic purification of the *E*/*Z*-isomers of a β,β-disubstituted α-enamide precursor was necessary before the catalytic asymmetric hydrogenation step.[23]

In order to support pharmacological and toxicological evaluations, it was necessary to supply multi-kilogram quantities of **1**. We have focused our attention on the development of an efficient and facile synthesis of optically active β-methyltryptophan ethyl ester (β-MeTrp-OEt, **2**) as a key-step of a manufacturing process for **1**. We investigated a straightforward route to (2*R*,3*S*)-**2** including two chirality control processes: crystallization-induced diastereomer transformation (CIDT), which is a hybrid process involving selective crystallization and in situ epimerization,[24,25] and optical resolution via diastereomeric salt formation. The drug candidate **1** contains an unsymmetrical urea structure with two chiral centers derived from **2**. We also studied a transformation of (2*R*,3*S*)-**2** to **1** involving a selective synthesis of unsymmetrical urea and a peptide coupling with minimal loss of the chiral integrity. Herein, we describe a practical synthesis of (2*R*,3*S*)- and (2*S*,3*R*)-**2** and an efficient transformation of (2*R*,3*S*)-**2** to **1**.

2. Results and discussion

2.1. Synthetic strategy

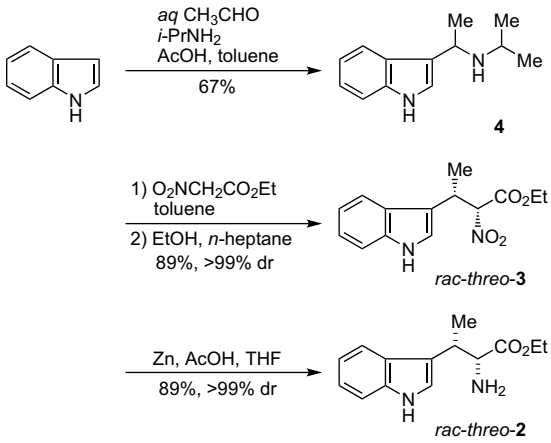
For the preparation of optically active β-MeTrp-OEt, the chirality control of the two asymmetric centers was the most critical issue. Our synthetic concept described herein is based on the following two key-steps (Scheme 1). The first is the diastereoselective preparation of racemic *threo*-α-nitro ester (*rac-threo*-**3**) via the CIDT process. Taking advantage of the highly acidic α-proton of the α-nitro ester, we attempted in situ epimerization of **3** during crystal growth. The other key-step is the resolution of racemic *threo*-β-MeTrp-OEt (*rac-threo*-**2**) via diastereomeric salt formation using a chiral acid. The resultant enantiopure (2*R*,3*S*)-**2** can be transformed into **1** via a couple of condensation reactions.[8]



Scheme 1. Strategic route to **1** via (2*R*,3*S*)-**2**.

2.2. Diastereoselective synthesis of *rac-threo*-2 via CIDT

A diastereomeric mixture of *rac-erythro*-**3** and *rac-threo*-**3** was readily prepared from indole by the modified Snyder's 'gramine chemistry' method using ethyl nitroacetate as nucleophile (Scheme 2). A one-pot aza-Friedel–Crafts (AFC) reaction of indole with acetaldehyde and *iso*-propylamine was reported to give gramine **4** in 39% yield.[11] To make the AFC reaction amenable for scale-up and to improve the yield, we carried out all operations at low temperature due to the thermodynamic instability of **4**.[26] Conducting the reaction and the work-up at 0–5 °C, **4** was consistently obtained in 67% yield.



Scheme 2. Diastereoselective synthesis of *rac-threo*-**2** via CIDT.

The *C*–*C* bond forming reaction of **4** with ethyl nitroacetate proceeded in a non-stereoselective manner to give **3** as a 6:4 diastereomeric mixture (*rac-threo*-**3**/*rac-erythro*-**3**).[12,27] It was reported that the methyl ester equivalent of *rac-threo*-**3** was obtained as a single diastereomer in >50% yield by recrystallization from 3:2 chloroform/hexane.[12] On the basis of this result, we anticipated that *rac-threo*-**3** could be diastereoselectively prepared via the CIDT process. Ethyl ester was chosen on the grounds that it had a higher melting point than methyl ester.

Each epimerization and crystallization process of **3** was investigated separately before the integrated process was optimized. Figure 2 shows the epimerization rate of *rac-threo*-**3** in ethanol with or without the addition of an equimolar amount of *iso*-propylamine. In the absence of amine, the diastereomeric mixture of *rac-erythro*-**3** and *rac-threo*-**3** reached equilibrium at 50 °C within 3 h, while only a slightly epimerized 9:1 mixture (*rac-threo*-**3**/*rac-erythro*-**3**) was obtained at 25 °C for 3 h, and no epimerization was observed at 0 °C. These results demonstrate that the epimerization rate in the absence of amine largely depends on the temperature

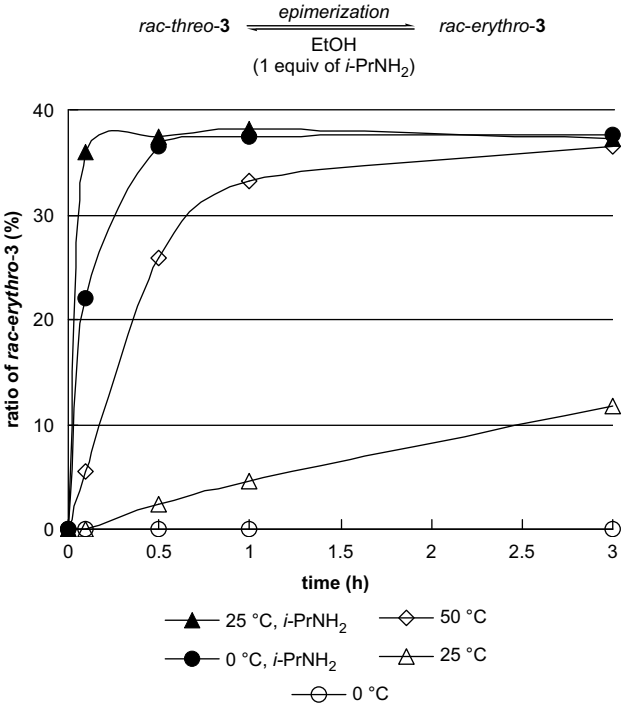
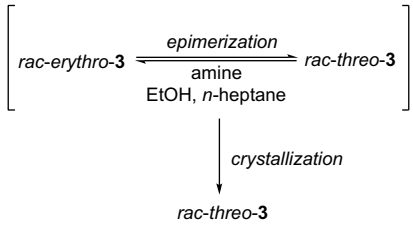


Figure 2. The rate enhancement effect achieved by amine addition.

and suggest that the rate at lower temperatures is not fast enough to achieve CIDT. In contrast, in the presence of amine, the mixture reached equilibrium at 25 °C within 0.1 h and even at 0 °C equilibrium was reached within 0.5 h. A crystallization study revealed that using 1:2 ethanol/*n*-heptane as the solvent, *rac-threo*-**3** crystallized in good yield while *rac-erythro*-**3** did not crystallize.

On the basis of these results, the CIDT process was optimized (Table 1). Adding 0.1 equiv of tertiary, secondary, or primary amine to the solution of a 6:4 equilibrium mixture (*rac-threo*-**3**/*rac-erythro*-**3**) in 1:2 ethanol/*n*-heptane achieved sufficient CIDT at 0 °C for 1 h. In particular, the addition of triethylamine or *iso*-propylamine was effective for CIDT and gave *rac-threo*-**3** in 94% yield with >99% dr (Entries 1 and 3). The slight decrease in the diastereomeric ratio in the case involving diethylamine was due to the formation of a crystalline diastereomixture adduct (*rac-threo*-**3**/*rac-erythro*-**3**/Et_2NH (1:1:2)) (Entry 2). When adding an equivalent of *iso*-propylamine, the desired diastereomer was obtained in only 50% yield (Entry 4). Possible reasons for the low yield with an equivalent of *iso*-propylamine include the higher solubility of *rac-threo*-**3** in the presence of *iso*-propylamine and the generation of a more soluble compound such as the adduct of *rac-threo*-**3** with *iso*-propylamine. These results suggest that a catalytic amount of amine is pivotal for the CIDT of **3**.

Table 1
Optimization of CIDT[a]



Entry	Amine		Crystals	
		Equiv	Yield	dr[b]
1	Et_3N	0.1	94	>99:1
2	Et_2NH	0.1	98	95:5
3	*i*-$PrNH_2$	0.1	94	>99:1
4	*i*-$PrNH_2$	1.0	50	>99:1

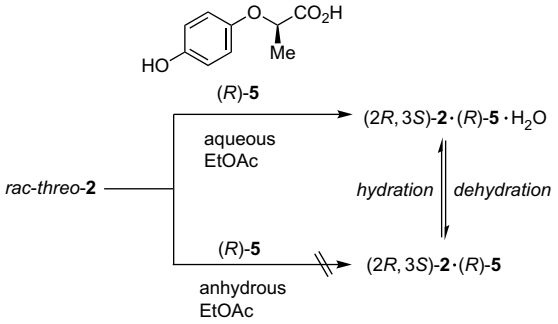
[a] CIDT was carried out at ambient temperature for 1 h using a 6:4 equilibrium mixture (*rac-threo*-**3**/*rac-erythro*-**3**).
[b] dr (*rac-threo*-**3**/*rac-erythro*-**3**) was determined by HPLC.[27]

Among these amines, *iso*-propylamine was the most suitable for this process, because it was released from **4** during the *C*–*C* bond forming reaction as a by-product and was able to be reused for CIDT. In fact, vacuum concentration of the *C*–*C* bond forming reaction mixture left a catalytic amount of *iso*-propylamine in the residue, and the residual *iso*-propylamine effectively catalyzed CIDT without the addition of further amine to afford *rac-threo*-**3** in 89% yield with >99% dr. The level of residual *iso*-propylamine was well controlled at approximately 0.1 equiv by continuous concentration of the reaction mixture with additional ethanol.

The subsequent nitro group reduction by Pd catalyzed hydrogenation suffered from epimerization and over-reduction, and the best conditions yielded only 60% of *rac-threo*-**2**. However, the reduction using zinc in THF/acetic acid successfully proceeded without epimerization to provide *rac-threo*-**2** in 89% yield with >99% dr.[28]

2.3. Resolution of *rac-threo*-2

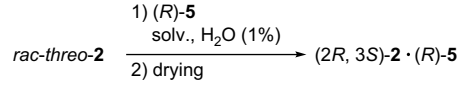
Then, the resolution of *rac-threo*-**2** via diastereomeric salt formation was investigated. Various types of chiral acids were evaluated for their potential as resolving agents for *rac-threo*-**2**.[29] The screening revealed that the lactic acid derivative (*R*)-2-(4-hydroxyphenoxy) propionic acid ((*R*)-**5**), which is used as raw material in agrochemicals[30] and liquid crystals,[31] was the most efficient resolving agent for *rac-threo*-**2**. The diastereomeric salt of (2*R*,3*S*)-**2** with (*R*)-**5** crystallized from ethyl acetate containing water, but not from anhydrous ethyl acetate (Scheme 3). Exposure of (2*R*,3*S*)-**2**·(*R*)-**5** to the moist atmosphere resulted in its conversion to monohydrate (2*R*,3*S*)-**2**·(*R*)-**5**·H_2O, which was easily re-converted to the anhydrous form by drying.[32] We speculated that the hydrate of the salt primarily crystallized.



Scheme 3. Diastereomeric salt formation of (2*R*,3*S*)-**2** with (*R*)-**5**.

On the basis of the necessity of water for the crystal growth, the resolving conditions were optimized with solvents containing water (Table 2). Using an equivalent of (*R*)-**5** to *rac-threo*-**2**, the salt was obtained in moderate yield (37%) with high optical purity (99% ee) from acetonitrile (Entry 1).[33] Reducing the level of (*R*)-**5** to a half equivalent gave the salt with the same optical purity (99% ee) but a decreased yield (28%) (Entry 2). The use of a half equivalent of resolving agent was so advantageous for large-scale preparation from the both economical and ecological viewpoints that we continued the optimization with a half equivalent of (*R*)-**5**.[34] While aqueous ketone solvents (acetone, 2-butanone (MEK), and 4-methylpentan-2-one (MIBK)) showed a downward yield tendency (Entries 3–5), aqueous ester solvents (methyl acetate, ethyl acetate, *n*-propyl acetate, and *n*-butyl acetate) showed an upward yield trend, which led to the improvement of resolution efficiency (Entries 6–9). In particular, the crystallization from *n*-butyl acetate containing 1% of water afforded the salt with the highest resolvability (*S*=0.85, Entry 9), which is commonly used as a measure of resolution efficiency.[35] Increasing the level of (*R*)-**5** to an equivalent did not give a significant improvement on resolvability (Entry 10).

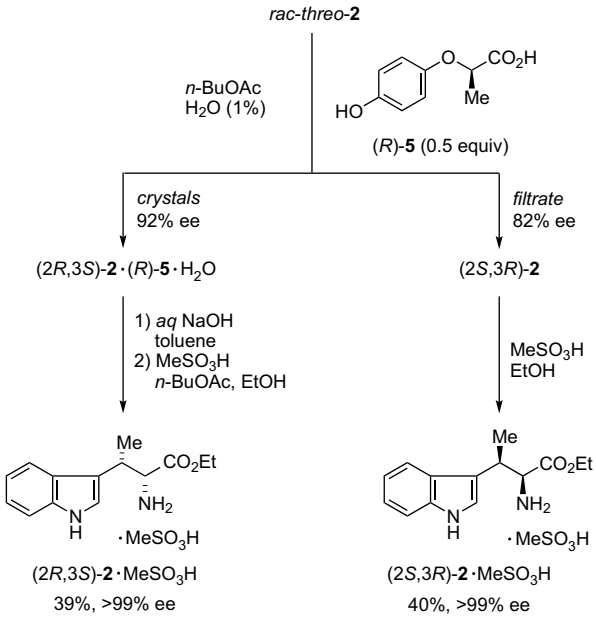
Table 2
Optimization of resolution



Entry	(*R*)-**5** equiv[a]	Solvent[b]	Yield[c] %	Optical purity % ee[d]	Resolvability *S*[e]
1	1.0	MeCN	37	99	0.73
2	0.5	MeCN	28	99	0.55
3	0.5	Acetone	21	95	0.40
4	0.5	MEK	17	90	0.31
5	0.5	MIBK	15	83	0.26
6	0.5	MeOAc	39	83	0.65
7	0.5	EtOAc	41	91	0.75
8	0.5	*n*-PrOAc	39	90	0.70
9	0.5	*n*-BuOAc	46	92	0.85
10	1.0	*n*-BuOAc	46	92	0.85

[a] Based on *rac-threo*-**2** used.
[b] Containing 1% of water.
[c] Isolated yield after drying based on *rac-threo*-**2** used.
[d] Enantiomeric excess of (2*R*,3*S*)-**2** was determined by HPLC.[33]
[e] *S*=yield (%)×2×optical purity (% ee)×10^{-4}.

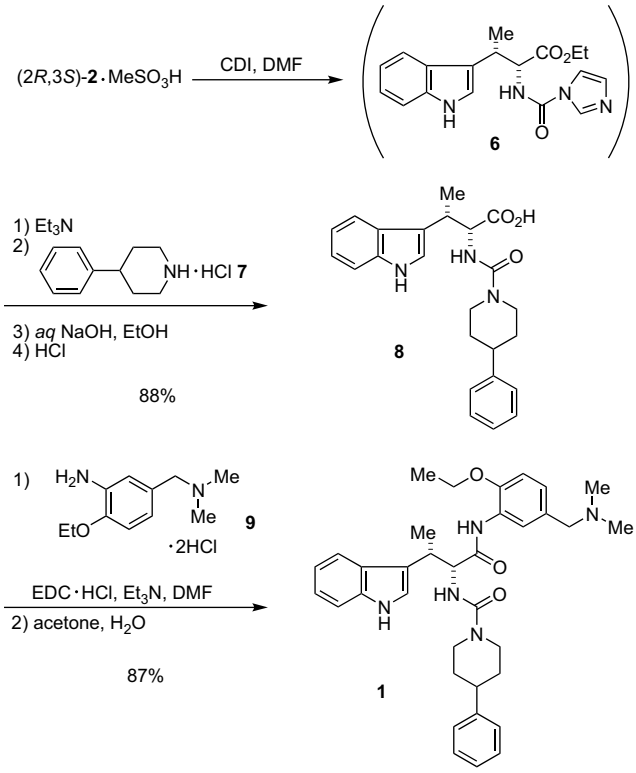
Fortunately, the optical purity was improved to >99% ee by the crystallization of the methanesulfonate of (2*R*,3*S*)-**2** (Scheme 4).[36] A resolution sequence involving diastereomeric salt formation, salt splitting, and methanesulfonate crystallization gave (2*R*,3*S*)-**2**·$MeSO_3H$ in 39% two-step yield with >99% ee. Meanwhile, the addition of methanesulfonic acid to the filtrate that was obtained during the diastereomeric salt formation step gave (2*S*,3*R*)-**2**·$MeSO_3H$ in 40% two-step yield with >99% ee. As a result, using only a half equivalent of (*R*)-**5** allowed both enantiomers to be simultaneously prepared with 79% total recovery from the racemate without any recycling process.



Scheme 4. Simultaneous preparation of both enantiomers using a half equivalent of resolving agent.

2.4. Synthesis of 1

Next, we investigated the transformation of (2*R*,3*S*)-**2** to **1** via an urea formation followed by a peptide coupling (Scheme 5). A wide variety of methods to prepare unsymmetrical ureas has been reported,[37–39] and, for instance, *N*-ureido-tryptophan esters were synthesized by a sequential displacement of the two imidazoles of *N*,*N*′-carbonyldiimidazole (CDI) with tryptophan esters and azacycles or by a similar method using *N*,*N*′-disuccinimidyl carbonate (DSC).[40,41] Though *N*-ureido-β-MeTrp **8** could be prepared with DSC in acetonitrile,[8] we attempted to apply readily available CDI to the urea forming reaction of (2*S*,3*R*)-**2**·$MeSO_3H$ with 4-phenylpiperidine hydrochloride (**7**),[42] which have no base-sensitive functions. The reaction conducted in acetonitrile involved issues of by-products, bis-adduct **10** and symmetrical urea **11** (Fig. 3). Fortunately, when the reaction was carried out in DMF **10** was not generated, although **11** was still formed. Whilst carefully observing the reaction, it was revealed that (2*R*,3*S*)-**2** was quantitatively converted into imidazolide **6** and that **11** was generated after the addition of weakly acidic substrate **7** to the resultant solution of **6**. These results suggested that **11** was formed by the reaction of **6** with (2*R*,3*S*)-**2** that was reconverted from **6** in the acidic reaction mixture. Therefore, to suppress the formation of **11**, we attempted to prevent the regeneration of (2*R*,3*S*)-**2** by the addition of amine. When 2.2 equiv of triethylamine were added prior to the addition of **7**, by-product **11** was formed in 7%. Increasing the level of triethylamine to 4.4 equiv successfully decreased the generation of **11** to 3%. The residual **11** was removed by the crystallization of



Scheme 5. Synthesis of **1**.

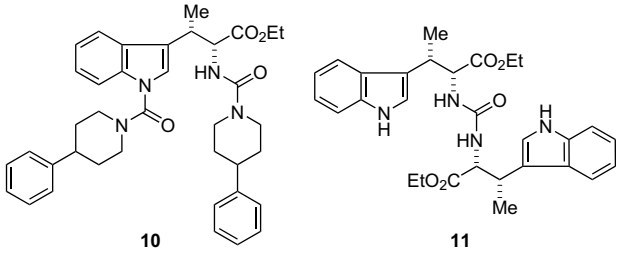


Figure 3. By-products identified in the urea forming reaction.

carboxylic acid **8** after one-pot hydrolysis of the ester group. As a result, **8** was obtained in 88% yield with >99% purity by HPLC area analysis and >99.9% ee.[43]

A typical peptide coupling reaction mediated by carbodiimides, such as 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (EDC), are known to be applicable to the condensation of *N*-ureido-α-amino acid with amine.[8,39–41] We conducted the final coupling reaction with EDC hydrochloride (EDC·HCl) and triethylamine in DMF. The reaction was completed within an hour at ambient temperature in the absence of 1-hydroxybenzotriazole (HOBt), which is known to promote the peptide coupling,[44,45] to give the target compound **1** with its epimer (1*S*,2*S*)-**1** as a major impurity. Neither adding HOBt, which is also known to suppress the racemization,[44] nor lowering the reaction temperature reduced the epimerization. Thus, to reduce the epimerization, we optimized the amount of triethylamine.[46] In the presence of 2 equiv of triethylamine to dihydochloric acid salt **9**, 2.6% of epimer was formed. Decreasing the level of triethylamine to an equivalent successfully reduced the generation of epimer to 0.8%. At least an equivalent of triethylamine was needed for the completion of the reaction.

After the reaction was carried out in the presence of an equivalent of triethylamine, adding aq sodium carbonate solution to the reaction mixture afforded the crystals of **1** that contained 0.8% of epimer. An extensive recrystallization study revealed that the use of

6:4 acetone/water at ambient temperature was effective at providing **1** in 87% yield with >99.9% purity by HPLC area analysis and >99.9% ee.[47] This process successfully provided kilogram quantities of drug candidate **1**, and the resulting products met all quality specifications.

3. Conclusion

We have developed the practical synthesis of (2*R*,3*S*)- and (2*S*,3*R*)-β-MeTrp-OEt **2**. The amine catalyzed CIDT of α-nitro ester **3** followed by the reduction of the nitro group without epimerization allowed the diastereoselective preparation of *rac-threo*-**2** with >99% dr. The diastereomeric salt formation using a half equivalent of resolving agent (*R*)-**5** in the presence of water followed by the crystallization of methanesulfonate simultaneously provided both (2*R*,3*S*)-**2**·$MeSO_3H$ and (2*S*,3*R*)-**2**·$MeSO_3H$ with >99% ee. We have also developed the efficient transformation of (2*R*,3*S*)-**2** to the diabetes drug candidate **1**. The selective synthesis of unsymmetrical urea **8** by suppressing the regeneration of (2*R*,3*S*)-**2** from imidazolide **6** followed by the peptide coupling with minimum epimerization successfully provided **1** in good yield with high quality.

4. Experimental section

4.1. General

All materials were purchased from commercial suppliers and used without further purification. Melting points were recorded on a Büchi B-540 micromelting apparatus and were uncorrected. IR spectra were recorded on a Horiba FT-210 spectrophotometer or Thermo Electron Nicolet 4700 spectrophotometer. NMR spectra were run at 300 MHz (^{1}H) and 75 MHz (^{13}C), respectively, on a Bruker DPX-300 spectrometer. Chemical shifts are reported as δ values using tetramethylsilane as an internal standard and coupling constants (*J*) are given in Hz. The following abbreviations are used: s=singlet, d=doublet, t=triplet, m=multiplet, br=broad. Optical rotation values were recorded on a JASCO DIP-370 polarimeter under standard conditions. HPLC analysis was performed with a Hitachi L-7000. Detection was performed with an ultraviolet absorption photometer (wavelength 254 nm). Purity was determined by HPLC and was presented as an area percentage of the compound peak relative to the total area of all the peaks. All compounds were judged to be of greater than 95% purity based upon ^{1}H NMR and HPLC analysis. The microanalyses and mass spectral analyses were carried out at Takeda Analytical Research Laboratories, Ltd.

4.2. Synthesis of *N*-[1-(1*H*-indol-3-yl)ethyl]propan-2-amine (4)

To a solution of indole (200.0 g, 1.71 mol) and acetic acid (800 mL) in toluene (200 mL) were successively added *iso*-propylamine (111.2 g, 1.88 mol) and 90% aq acetaldehyde (87.6 g, 1.79 mol) at 0–10 °C. The mixture was stirred at 0–5 °C for 23 h. After adding water (2.0 L) and ethyl acetate (280 mL), the layers were separated. Then, 30% aq NaOH (1.85 L) was added dropwise to the aqueous layer at 0–10 °C, and the mixture was stirred at 0–5 °C for 1 h. The resultant precipitate was collected by filtration, washed with water (1.0 L), and dried in vacuo to give **4** (230.0 g, 1.14 mol, 67% yield) as a pale orange crystalline powder. Mp 115–117 °C; IR (ATR) ν 1451, 1097, 791, 732, 686 cm^{-1}; MS (ESI) *m*/*z* 201 $(M-H)^-$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (br s, 1H), 7.74 (d, *J*=7.8 Hz, 1H), 7.38 (d, *J*=8.0 Hz, 1H), 7.25–7.15 (m, 2H), 7.11 (d, *J*=2.4 Hz, 1H), 4.30 (q, *J*=2.4 Hz, 1H), 2.97–2.84 (m, 1H), 1.55 (d, *J*=6.6 Hz, 1H), 1.44 (br s, 1H), 1.11 (t, *J*=5.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.7, 126.3, 122.0, 121.0, 120.9, 119.3, 119.2, 111.4, 47.5, 45.9, 23.8, 23.3, 23.0. Anal. Calcd for $C_{13}H_{18}N_2$: C, 77.18; H, 8.97; N, 13.85. Found: C, 77.06; H, 9.24; N, 13.83.

4.3. Synthesis of *threo* ethyl 3-(1*H*-indol-3-yl)-2-nitrobutanoate (*rac-threo*-3)

To a suspension of **4** (55.0 g, 272 mmol) in toluene (220 mL) was added ethyl nitroacetate (38.0 g, 289 mmol). The mixture was stirred at 95 °C for 1 h. After cooling to room temperature, the mixture was concentrated in vacuo. Ethanol (110 mL) was added to the residue, and the resultant mixture was concentrated in vacuo (twice). Then, ethanol (110 mL) was added to the residue, and the mixture was stirred at 60 °C until a clear solution was obtained. After cooling to room temperature, *n*-heptane (220 mL) was added dropwise to the mixture. Then the mixture was stirred at 0 °C for 1 h. The resultant precipitate was collected by filtration, washed with ice-cooled 1:4 ethanol/*n*-heptane (220 mL), and dried in vacuo to give *rac-threo*-**3** (66.9 g, 242 mmol, 89% yield, >99% dr) as a white crystalline powder. Mp 117–119 °C; IR (ATR) ν 3368, 1727, 1548, 1542, 742 cm^{-1}; MS (ESI) *m*/*z* 277 $(M+H)^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (br s, 1H), 7.66 (d, *J*=8.0 Hz, 1H), 7.39 (d, *J*=8.0 Hz, 1H), 7.27–7.15 (m, 2H), 7.10 (d, *J*=2.5 Hz, 1H), 5.47(d, *J*=9.1 Hz, 1H), 4.26–4.19 (m, 1H), 4.06–3.95 (m, 2H), 1.58 (d, *J*=7.0 Hz, 3H), 0.98 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.8, 136.2, 125.9, 122.6, 122.4, 120.0, 118.8, 113.9, 111.5, 92.9, 62.7, 33.2, 17.8, 13.5. Anal. Calcd for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.93; H, 5.98; N, 10.27.

4.4. Synthesis of *threo* ethyl 2-amino-3-(1*H*-indol-3-yl)butanoate (*rac-threo*-2)

To a solution of acetic acid (10 mL) in THF (5 mL) were successively added zinc dust (9.48 g, 145 mmol) and a solution of *rac-threo*-**3** (2.00 g, 7.24 mmol, >99% dr) and acetic acid (5 mL) in THF (10 mL) at 0–10 °C. The mixture was stirred at room temperature for 18 h. The precipitate was filtered off and washed with THF (10 mL). The combined filtrates were concentrated in vacuo. After adding ethyl acetate (20 mL) and 5% aq $NaHCO_3$ (80 mL) to the residue, the layers were separated. The aqueous layer was extracted with ethyl acetate (10 mL), and the combined organic layers were concentrated in vacuo. Ethyl acetate (2 mL) was added to the residue, and then *n*-heptane (6 mL) was added dropwise to the resultant solution at room temperature. After stirring at 0 °C for 1 h, the resultant precipitate was collected by filtration, washed with ice-cooled 1:3 ethyl acetate/*n*-heptane (3 mL), and dried in vacuo to give *rac-threo*-**2** (1.59 g, 6.46 mmol, 89% yield, >99% dr) as a white crystalline powder. Mp 82–83 °C; IR (ATR) ν 1736, 1217, 1157, 1115, 744 cm^{-1}; MS (ESI) *m*/*z* 247 $(M+H)^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 (br s, 1H), 7.47 (d, *J*=7.8 Hz, 1H), 7.37 (d, *J*=7.9 Hz, 1H), 7.25–7.13 (m, 2H), 7.06 (d, *J*=2.1 Hz, 1H), 4.25–4.17 (m, 2H), 3.94 (d, *J*=4.1 Hz, 1H), 3.72–3.67 (m, 1H), 1.40 (br s, 1H), 1.36 (d, *J*=7.1 Hz, 3H), 1.27 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.8, 136.2, 125.9, 122.6, 122.4, 112.0, 118.8, 113.9, 111.5, 92.9, 62.7, 33.2, 17.8, 13.5. Anal. Calcd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.19; H, 7.40; N, 11.60.

4.5. Synthesis of ethyl (2*R*,3*S*)-2-amino-3-(1*H*-indol-3-yl)butanoate (*R*)-2-(4-hydroxyphenoxy)propionate hydrate ((2*R*,3*S*)-2·(*R*)-5·H_2O)

To a solution of (*R*)-**5** (1.85 g, 10.2 mmol) and water (0.5 mL) in *n*-butyl acetate (50 mL), *rac-threo*-**2** (5.00 g, 20.3 mmol) was added. The mixture was stirred at room temperature for 4 h. The resultant precipitate was collected by filtration, washed with *n*-butyl acetate (10 mL), and dried under a stream of air to give (2*R*,3*S*)-**2**·(*R*)-**5**·H_2O (4.20 g, 9.41 mmol, 46% yield based on *rac-threo*-**2**, 92% ee) as a white crystalline powder. Mp 133–134 °C; IR (ATR) ν 1747, 1590, 1476, 1209, 749 cm^{-1}; MS (ESI) *m*/*z* 247 $(M+H)^+$; $[\alpha]_D^{20}$ +11.1 (*c* 1.02, MeOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.85 (s, 1H), 7.51 (d,

J=7.8 Hz, 1H), 7.33 (d, J=8.0 Hz, 1H), 7.14 (d, J=2.3 Hz, 1H), 7.06–6.94 (m, 1H), 6.70–6.62 (m, 1H), 4.57 (q, J=6.7 Hz, 1H), 3.98–3.90 (m, 2H), 3.63 (d, J=6.8 Hz, 1H), 3.39–3.30 (m, 1H), 1.42 (d, J=6.8 Hz, 3H), 1.29 (d, J=7.1 Hz, 3H), 1.00 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 174.4, 174.3, 151.9, 151.0, 136.8, 126.8, 123.1, 121.4, 118.9, 118.7, 116.6, 116.4, 116.1, 111.9, 73.3, 60.5, 59.4, 35.0, 19.0, 16.4, 14.3. Anal. Calcd for $C_{23}H_{28}N_2O_6\cdot H_2O$: C, 61.87; H, 6.77; N, 6.27. Found: C, 61.74; H, 6.77; N, 6.20.

4.6. Synthesis of ethyl (2*R*,3*S*)-2-amino-3-(1*H*-indol-3-yl)butanoate methanesulfonate ((2*R*,3*S*)-**2**·MeSO$_3$H)

To a mixture of toluene (5.0 mL) and 1 M aq NaOH (5.0 mL) was added (2*R*,3*S*)-**2**·(*R*)-**5**·H$_2$O (1.00 g, 2.24 mmol, 92% ee). After separating the layers, the organic layer was washed with water (5.0 mL) and concentrated in vacuo. *n*-Butyl acetate (5.0 mL) and ethanol (0.5 mL) were added to the residue, and then methanesulfonic acid (215 mg, 2.68 mmol) was added dropwise to the resultant solution at room temperature. After stirring at room temperature for 2 h, the resultant precipitate was collected by filtration, washed with 10:1 *n*-butyl acetate/ethanol (1.0 mL), and dried in vacuo to give (2*R*,3*S*)-**2**·MeSO$_3$H (648 mg, 1.89 mmol, 84% yield based on (2*R*,3*S*)-**2**·(*R*)-**5**·H$_2$O, >99% ee) as a white crystalline powder. Mp 129–130 °C; IR (KBr) ν 3298, 1743, 1520, 1205, 1184 cm^{-1}; MS (FAB) m/z 247 (M+H)$^+$; $[\alpha]_D^{20}$ +6.1 (c 0.97, MeOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.08 (s, 1H), 8.32 (s, 1H), 7.51 (d, J=7.8 Hz, 1H), 7.39 (d, J=8.0 Hz, 1H), 7.22 (d, J=2.3 Hz, 1H), 7.10 (t, J=7.5 Hz, 1H), 7.01 (t, J=7.4 Hz, 1H), 4.16 (d, J=6.5 Hz, 1H), 4.04–3.92 (m, 2H), 3.67–3.58 (m, 1H), 2.34 (s, 3H), 1.45 (d, J=7.2 Hz, 3H), 0.96 (d, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.8, 137.2, 126.8, 124.5, 122.1, 119.4, 119.1, 113.5, 112.5, 62.4, 58.1, 40.6, 33.1, 17.3, 14.4. Anal. Calcd for $C_{15}H_{22}N_2O_5S$: C, 52.62; H, 6.48; N, 8.18; S, 9.36. Found: C, 52.44; H, 6.44; N, 8.04; S, 9.33.

4.7. Synthesis of ethyl (2*S*,3*R*)-2-amino-3-(1*H*-indol-3-yl)butanoate methanesulfonate ((2*S*,3*R*)-**2**·MeSO$_3$H)

To a solution of (*R*)-**5** (1.85 g, 10.2 mmol) and water (0.5 mL) in *n*-butyl acetate (50 mL) was added *rac-threo*-**2** (5.00 g, 20.3 mmol). The mixture was stirred at room temperature for 4 h. The resultant precipitate was filtered off and washed with *n*-butyl acetate (10 mL). Ethanol (5.0 mL) and methanesulfonic acid (980 mg, 12.2 mmol) were successively added dropwise to the combined filtrates at room temperature. After stirring at room temperature for 2 h, the resultant precipitate was collected by filtration, washed with 10:1 *n*-butyl acetate/ethanol (11 mL), and dried in vacuo to give (2*S*,3*R*)-**2**·MeSO$_3$H (2.76 g, 8.06 mmol, 40% yield based on *rac-threo*-**2**, >99% ee) as a white crystalline powder. Mp 129–130 °C; IR (ATR) ν 1742, 1517, 1163, 1044, 743 cm^{-1}; MS (ESI) m/z 247 (M+H)$^+$; $[\alpha]_D^{20}$ −6.5 (c 1.03, MeOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.08 (s, 1H), 8.27 (s, 1H), 7.50 (d, J=7.8 Hz, 1H), 7.38 (d, J=8.0 Hz, 1H), 7.21 (d, J=2.4 Hz, 1H), 7.09 (t, J=7.1 Hz, 1H), 7.00 (t, J=7.1 Hz, 1H), 4.15 (d, J=6.5 Hz, 1H), 4.04–3.93 (m, 2H), 3.66–3.57 (m, 1H), 2.34 (s, 3H), 1.44 (d, J=7.2 Hz, 3H), 0.95 (d, J=7.1 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 169.5, 136.9, 126.5, 124.2, 121.7, 119.1, 118.7, 113.2, 112.2, 62.0, 57.7, 40.3, 32.8, 17.0, 14.0. Anal. Calcd for $C_{15}H_{22}N_2O_5S$: C, 52.62; H, 6.48; N, 8.18; S, 9.36. Found: C, 52.59; H, 6.44; N, 8.23; S, 9.43.

4.8. Synthesis of (2*R*,3*S*)-3-(1*H*-indol-3-yl)-2-[(4-phenylpiperidine-1-carbonyl)amino]butyric acid (8)

To a solution of CDI (2.09 g, 12.9 mmol) in DMF (12 mL) was added a solution of (2*R*,3*S*)-**2**·MeSO$_3$H (4.00 g, 11.7 mmol) in DMF (12 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h. Triethylamine (5.21 g, 51.5 mmol) and 4-phenylpiperidine hydrochloride (2.55 g, 12.9 mmol) were successively added at 0–10 °C. The mixture was allowed to warm and stirred at room temperature for 2.5 h. After adding water (24 mL) and ethyl acetate (24 mL), the layers were separated. The aqueous layer was extracted with ethyl acetate (24 mL). The combined organic layers were successively washed with 1 M hydrochloric acid (2×24 mL) and water (2×24 mL) and then concentrated in vacuo. Ethanol (24 mL) was added to the residue, and the resultant solution was concentrated in vacuo. After the addition of ethanol (40 mL), 4 M aq NaOH (8 mL) was added dropwise to the resultant solution. The mixture was stirred at room temperature for 4 h. Then, 4 M hydrochloric acid (12 mL) was added dropwise to the mixture. After stirring at 0 °C for 1.5 h, the resultant precipitate was collected by filtration, washed with ice-cooled ethanol/water (12 mL, 2:1), and dried in vacuo to give **8** (4.17 g, 10.3 mmol, 88% yield, >99.9% ee,) as a white crystalline powder. Mp 162–167 °C (decomp.); IR (KBr) ν 1736, 1581, 1512, 1194, 754 cm^{-1}; MS (FAB) m/z 406 (M+H)$^+$; $[\alpha]_D^{20}$ +42.0 (c 1.04, MeOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.23 (br s, 1H), 10.82 (s, 1H), 7.56 (d, J=7.7 Hz, 1H), 7.35–7.27 (m, 3H), 7.20–7.16 (m, 4H), 7.08–7.03 (m, 2H), 6.29 (d, J=8.5 Hz, 1H), 4.50 (dd, J=8.2, 7.3 Hz, 1H), 4.11 (t, J=14.3 Hz, 2H), 3.59 (t, J=7.1 Hz, 1H), 2.79–2.62 (m, 3H), 1.69 (d, J=12.1 Hz, 2H), 1.49–1.34 (m, 5H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 174.9, 158.2, 146.8, 137.0, 129.3, 127.5, 127.4, 127.0, 123.2, 121.6, 119.4, 119.1, 117.2, 112.3, 59.6, 45.3, 45.2, 42.7, 33.7, 33.6, 33.1, 18.3. Anal. Calcd for $C_{24}H_{27}N_3O_3\cdot 0.1H_2O$: C, 70.77; H, 6.73; N, 10.32. Found: C, 70.75; H, 6.85; N, 10.27.

4.9. Synthesis of *N*-[(1*R*,2*S*)-1-({5-[(dimethylamino)methyl]-2-ethoxyphenyl}aminocarbonyl)-2-(1*H*-indol-3-yl)propyl]-4-phenyl-1-piperidinecarboxamide (1)

To a solution of **8** (700 g, 1.73 mol) and **9** (462 g, 1.73 mol) in DMF (3.45 L), triethylamine (175 g, 1.73 mol) and EDCl (397 g, 2.07 mol) were successively added at room temperature. The mixture was stirred at room temperature for 1 h. Then, 2 M aq NaOH (1.73 L) and 5% aq Na_2CO_3 (1.73 L) were successively added. After stirring at room temperature for 1.5 h, the resultant precipitate was collected by filtration, washed with water (6.9 L), and dried in vacuo to give crude-**1** (1004 g, 1.73 mol, 100% yield) as a white crystalline powder. To a solution of water (1.0 L) in acetone (9.0 L) was added crude-**1** (1004 g, 1.73 mol). The solution was filtered to remove any insoluble dust, which was rinsed with 10:1 acetone/water (3.3 L). Water (6.7 L) was added dropwise to the combined filtrates at room temperature. After stirring at room temperature for 4 h, the resultant precipitate was collected by filtration, washed with 1:1 acetone/water (4 L), and then dried in vacuo to give **1** (880 g, 1.51 mol, 87% yield, >99.9% ee) as a white crystalline powder. Mp 164–165 °C; IR (KBr) ν 3361, 1666, 1219, 733 cm^{-1}; MS (FAB) m/z 582 (M+H)$^+$; $[\alpha]_D^{20}$ +4.0 (c 1.01, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (br s, 1H), 8.25 (d, J=1.9 Hz, 1H), 8.05 (s, 1H), 7.79 (d, J=7.6 Hz, 1H), 7.37–7.06 (m, 8H), 6.96 (dd, J=8.3, 2.0 Hz, 1H), 6.73 (d, J=8.3 Hz, 1H), 5.43 (d, J=7.6 Hz, 1H), 4.94 (t, J=7.4 Hz, 1H), 4.17 (d, J=13.2 Hz, 1H), 4.04 (d, J=13.3 Hz, 1H), 3.98–3.82 (m, 2H), 3.75–3.66 (m, 1H), 3.36 (s, 2H), 2.95–2.79 (m, 2H), 2.71–2.61 (m, 1H), 2.46–2.31 (m, 1H), 2.24 (s, 6H), 1.84 (d, J=12.0 Hz, 2H), 1.73–1.51 (m, 5H), 1.26 (t, J=7.0 Hz, 3H); ^{13}C NMR(75 MHz, $CDCl_3$) δ 170.5, 157.6, 146.8, 145.9, 136.9, 131.6, 128.9, 127.4, 127.2, 127.0, 126.8, 124.7, 122.4, 121.1, 119.9, 119.7, 117.2, 111.7, 111.1, 64.6, 64.3, 60.7, 45.6, 45.2, 45.1, 43.0, 35.2, 33.4, 33.3, 18.2, 15.1. Anal. Calcd for $C_{35}H_{43}N_5O_3$: C, 72.26; H, 7.45; N, 12.04. Found: C, 71.97; H, 7.39; N, 11.95.

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28. The dr of **2** was determined by HPLC. HPLC conditions: column: Chiralcel OJ-R (4.6×150 mm); mobile phase: 0.05 M aq KH_2PO_4 (pH 7.0)/MeCN (70: 30); flow rate: 0.5 mL/min; column temperature: 15 °C; detection: UV 254 nm.
29. For example, the diastereomeric salt of (2*R*,3*S*)-**2** with an equivalent of *O*,*O*′-diacetyl-L-tartaric acid was obtained in 76% ee and 44% yield from 9:1 2-propanol/water (*S*=0.67).
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33. The optical purity of **2** was determined by HPLC. HPLC conditions: column: Chiralcel OJ-RH (4.6×150 mm); mobile phase: 0.05 M aq KH_2PO_4 (pH 6.5)/MeCN (75:25); flow rate: 0.5 mL/min; column temperature: 15 °C; detection: UV 254 nm. The absolute configuration of **2** was assigned by a comparison of H-β-MeTrp-OH derivatized from **2** with an authentic sample by chiral column HPLC. For the HPLC separation of the enantiomers of β-MeTrp, see: Peter, A.; Torok, G.; Armstrong, D. W.; Toth, G.; Tourwe, D. *J. Chromatogr. A* **2000**, *904*, 1–15. HPLC conditions: column: Chirobiotic R (4.6×250 mm); mobile phase: H_2O/MeOH (70:30); flow rate: 0.75 mL/min; column temperature: 15 °C; detection: UV 254 nm.
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