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First enantioselective synthesis of the novel antiinfective TAN-1057A via its aminomethyl-substituted dihydropyrimidinone heterocycle

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Dedicated to Professor Dieter Seebach

Abstract—Enantiomerically pure N^2-*Z*-N^2-MeAsnOH [(*S*)-**14**], prepared in 8 steps (23% overall yield) from asparaginic acid, was first subjected to a Hofmann degradation with $PhI(OCOCF_3)_2$ yielding (*S*)-N^2-*Z*-N^2-methyl-2,3-diaminopropanoic acid [N^2-*Z*-N^2-Me-*L*-A_2pr, (*S*)-**15**], and this in turn was protected to give N^2-*Z*-N^3-Boc-N^2-Me-*L*-A_2pr [(*S*)-**17**]. Condensation of (*S*)-**17** with HN=C(SMe)NHCONH$_2$ followed by removal of the *tert*-butoxycarbonyl protecting group, cyclization and hydrogenolytic removal of the Z-group gave the heterocycle of TAN-1057A [(*S*)-**1**] with an e.e. of 87 in 36% yield [from (*S*)-**14**]. Coupling of (*S*)-**1** with (*S*)-tris-Z-β-homoarginine (**20a**) in the presence of *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU) and iPr_2NEt in *N*,*N*-dimethylacetamide followed by hydrogenolysis afforded the most active A-diastereomer of the natural antibiotic TAN-1057 in 52% yield (from (*S*)-**1** and **20a**). Similarly, starting from (*S*)-**1**, a single diastereomer of the potent, less toxic TAN-1057A analogue **22b** with a β-lysine side chain has been prepared. All described synthetic steps do not require column chromatography for purification of the products.

1. Introduction

A mixture of diastereomers of the very potent antibiotics TAN-1057A/B was first isolated by Japanese scientists at the Takeda company from the culture broth of *Flexibacter* sp. PK-74.[1] These compounds were found to be highly active against methicillin-resistant *Staphylococcus aureus* (MRSA) strains.[1,2] Both main components of this mixture were found to be dipeptides with an (*S*)-β-homoarginine side chain attached to a dihydropyrimidinone heterocyclic moiety.[2] The Takeda group succeeded in separating the natural diastereomeric mixture of TAN-1057A/B (6.0 g) into two fractions and isolated TAN-1057A (1.56 g) and TAN-1057B (5 mg) as dihydrochlorides.[2]

The absolute configurations at C-5 for both epimers of TAN-1057A/B were assigned on the basis of the similarities in the CD spectra which were recorded for the product obtained by mild hydrolysis (2% aq. Na_2CO_3, 70 °C, 1 h) of TAN-1057A (acyclic dipeptide **2**), and the model compound **3** with its known (*S*)-configuration at C-2 (Fig. 1).[2]

(*S*)-Configuration of C-5 in the heterocyclic portion of the molecule was assigned to TAN-1057A, while (*R*)-configuration of C-5 was attributed to TAN-1057B. Epimerization at C-5 in TAN-1057A occurs in MeOH in the presence of MeONa, or during heating in aqueous HCl. Acidic degradation of the molecule yields derivatives of *N*-methyl-2,3-diaminopropionic acid, a constituent amino acid of the TAN-1057 heterocycle.

The first successful synthesis of TAN-1057A/B in which an attempt to prepare TAN-1057A as a single diastereomer was made, instead resulted in a diastereomeric mixture of TAN-1057A and B due to the lability of the 2,3-diaminopropionic acid to epimerization.[3] Before embarking on the present study, it was not clear, whether this stereogenic center is configurationally stable enough to allow for a total synthesis of the enantiomerically pure material in vitro.

Keywords: Total synthesis; Amino acids; Chiral pool; Nitrogen heterocycles; Natural products.
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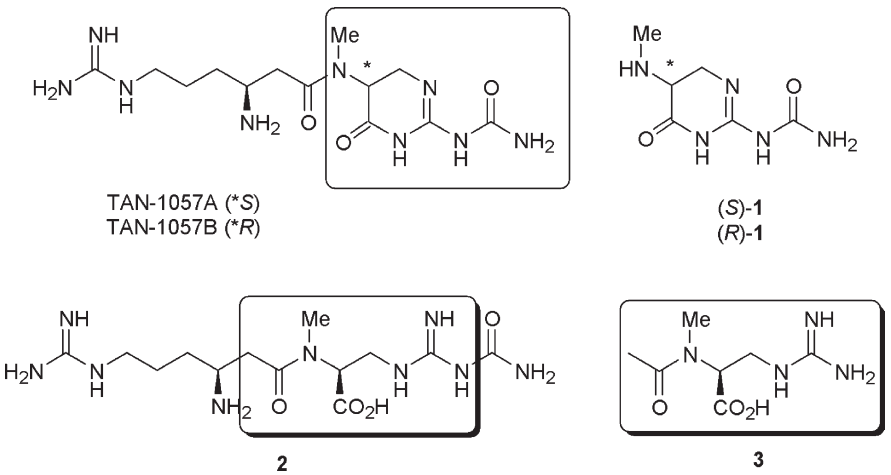


Figure 1. Structures and absolute configurations of TAN-1057A/B and the dihydropyrimidinone derivative **1** contained therein.

Up to now, most of the unique biological activity data have been determined for the diastereomeric mixture of TAN-1057A,B. For example, no cross-resistance between TAN-1057A,B and methicillin, erythromycin and gentamycin was found. TAN-1057A was shown to be by a factor of 2–4 more potent against Gram-positive and Gram-negative bacteria than TAN-1057B.[1,2] TAN-1057A is efficient against all of the MRSA strains evaluated, and was found to compare very favorably to vancomycin in an in vivo infection model.[1] Therefore, for further tests it was deemed necessary to elaborate a stereoselective access to either diastereomer of TAN-1057. This synthetic procedure should also be applicable for the facile preparation of diastereomerically pure analogues of TAN-1057[4] with improved properties (more active, less toxic) and therefore might lead to the discovery of new therapeutically useful drugs. We have reported convenient, convergent syntheses of TAN-1057 A/B and its analogues with various side chains[4b–e] utilizing the heterocycle **1** as a starting material.[5]

In designing a synthetic strategy towards the enantiomerically pure heterocycle (*S*)-**1**, the known facile racemization of N^2-methyl-2,3-diaminopropionic acid derivatives had to be taken into account,[3] therefore a reliable approach to the suitably protected N^2-methyl-2,3-diaminopropionic acid (N^2-Me-*L*-A_2pr) in enantiomerically pure form was the key issue.

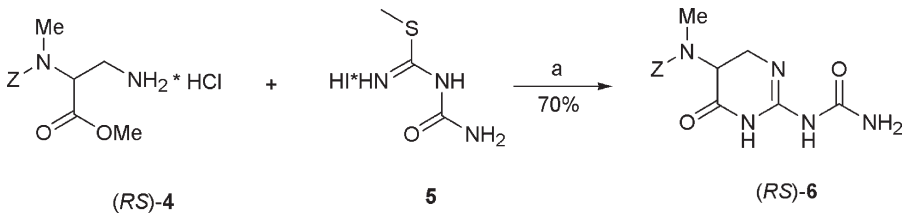
2. Results and discussion

2.1. Enantioselective synthesis of the heterocycle in TAN-1057A

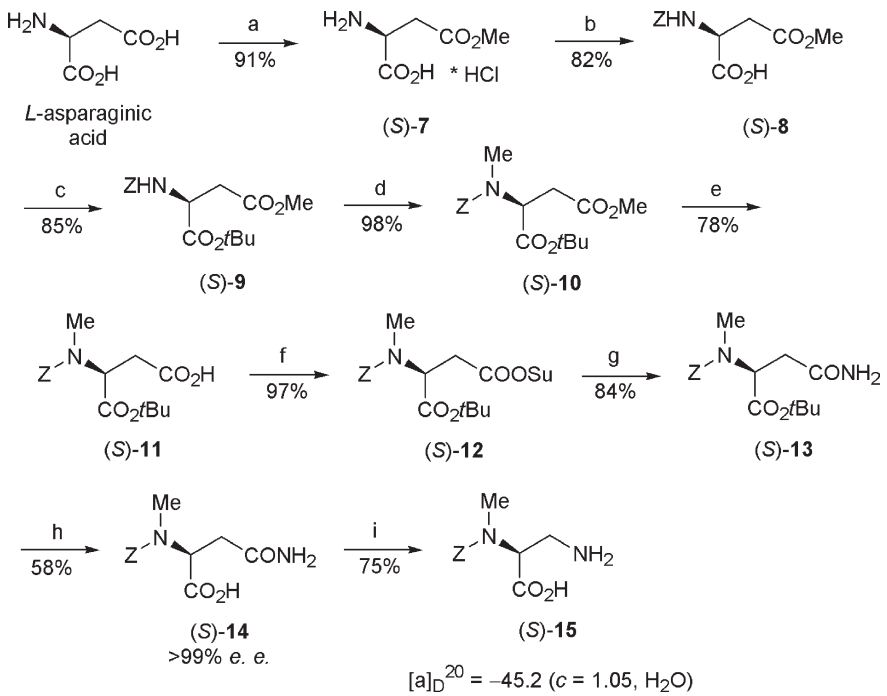
The racemic heterocycle (*RS*)-**1** was prepared by condensation of N^2-Z-N^2-Me-A_2prOMe [(*RS*)-**4**] with 2-methyl-2-thiopseudobiuret hydroiodide (**5**) and subsequent removal of the Z-protecting group from the resulting (*RS*)-**6** (Scheme 1) by hydrogenolysis.[5]

With a similar approach to the enantiomerically pure heterocycle (*S*)-**1** in mind, optically pure N^2-Z-*L*-A_2pr and N^2-Boc-*L*-A_2pr were prepared from the correspondingly protected asparagines.[7] In order to be able to create the 2,3-diaminopropionic acid fragment at a later step of the synthesis, N^2-Z-N^2-Me-*L*-AsnOH was needed. Selective N^2-methylation of asparagine is not possible, unless the amido group ($CONH_2$) is blocked. Therefore, the simplest way to overcome this difficulty was to use the aspartic acid with an appropriate protection which discriminates the two carboxyl groups, and then, after performing the mono *N*-methylation, to transform the terminal carboxyl group into its corresponding amide. Thus, *L*-aspartic acid was first converted into Z-*L*-Asp(OMe)OH [(*S*)-**8**][8] which was then protected by the formation of the *tert*-butyl ester (*S*)-**9** (Scheme 2).[9]

N-Methylation of (*S*)-**9** was achieved with methyl iodide in DMF in the presence of silver(I) oxide as a base according to the known method.[10] As stated in the original publication, no racemization was detected under these conditions. Nevertheless, due to the strong basicity of Ag_2O, this step as well as the next one, are the most dangerous in this respect. Saponification of the methyl ester (*S*)-**10** was performed carefully by slow addition of a slight excess of lithium hydroxide solution at +5 °C. The acid (*S*)-**11** may be converted into the amide (*S*)-**13** in a one pot operation by treatment first with *N*-hydroxybenzotriazole (HOBt) and *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide (EDC) in THF at 0 °C, and then with conc. aq. NH_3. However, it is



Scheme 1. Improved conditions of the one-step cyclization to the racemic heterocycle (*RS*)-**10**: (a) AcONa, MeCN, 55 °C, 48 h.[6]



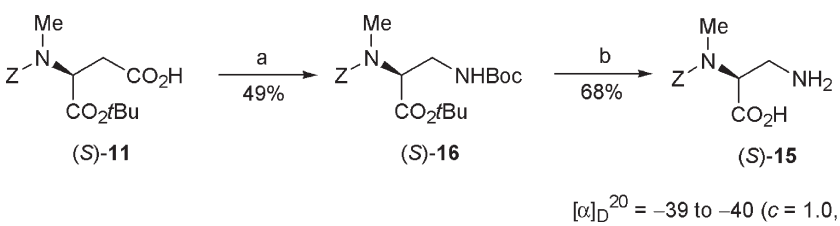
Scheme 2. Stereoselective synthesis of N^2-benzyloxycarbonyl-N^2-methyl-*L*-asparagine (N^2-Z-N^2-Me-*L*-AsnOH, (*S*)-**14**) and (*S*)-3-amino-2-(*N*-benzyloxycarbonyl-*N*-methyl)aminopropionic acid (N^2-Z-N^2-Me-*L*-A_2pr, (*S*)-**15**): (a) $SOCl_2$, MeOH, −10→+20 °C, 25 min; (b) ZCl, MgO, H_2O/ether, +5 °C, 6 h; (c) isobutene, conc. H_2SO_4, CH_2Cl_2, 20 °C, 48 h; (d) MeI (7 equiv.), Ag_2O (1.02 equiv.), DMF, 20 °C, 7 h; (e) LiOH (1.0 equiv.), MeOH/H_2O, +5→20 °C; (f) *N*-hydroxysuccinimide (1.1 equiv.), EtOAc, DCC (1.1 equiv.) in dioxane, +5 °C, overnight; (g) aq. NH_3, THF, 0 °C; (h) TFA, CH_2Cl_2, 20 °C, 4 h; (i) $PhI(OCOCF_3)_2$, DMF/H_2O, pyridine, 20 °C, 16 h.

better to first transform (*S*)-**11** into the crystalline *O*-succinimidyl ester (*S*)-**12**. With this, two goals were achieved: firstly, the ester (*S*)-**12** could be easily purified by recrystallization from a dioxane/ether mixture, and, secondly, the ω-carboxyl group was activated for subsequent conversion to the amide. Afterwards, the α-carboxyl group in (*S*)-**13** was deprotected under standard conditions, and the key intermediate N^{α}-Z-N^{α}-MeAsnOH [(*S*)-**14**] was isolated. In several experiments the enantiomeric excess of the crude (*S*)-**14** was always found to be about 77% (HPLC analysis on a chiral stationary phase; see Section 4 for details). Therefore, considerable racemization must have taken place at an earlier stage. Luckily, the optical purity could easily be restored after recrystallization from an *i*PrOH/EtOAc mixture. The racemic mixture (*RS*)-**14** (mp 160–162 °C) is much less soluble in *i*PrOH and water, and therefore the soluble fraction contains mostly the material with high enantiomeric excess. By this procedure, optically pure (*S*)-**14** (>99% e.e.) was obtained in 58% yield after one or two recrystallizations (mp 129 °C). When this work was completed, a general approach to *N*-methylamino acids by way of intermediate 5-oxazolidinones appeared in print.[11]

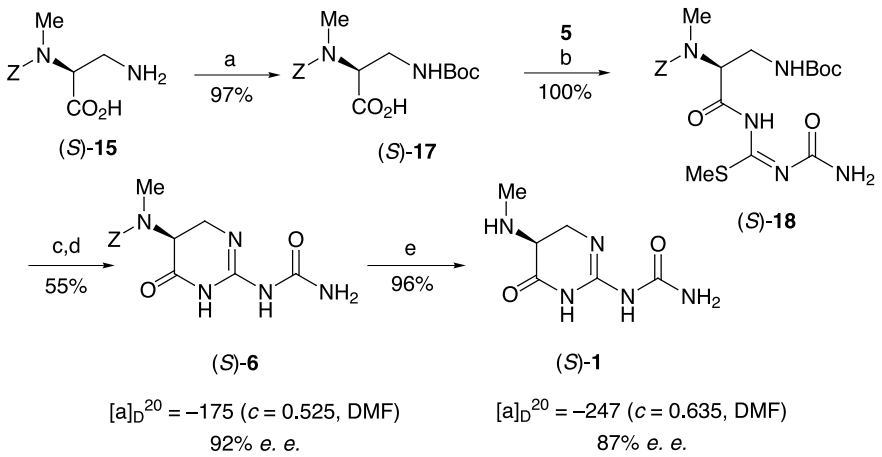
By this published approach, compound (*S*)-**14** has been prepared in only 4 steps.[11a] However, two of these four steps require column chromatography, certainly a drawback, when scale-up would be required.[12]

Direct amidation of the methyl ester (*S*)-**10** with methanolic ammonia was found to be difficult, as it required prolonged heating at about 100 °C, or the reaction with liquid ammonia at room temperature.[13] Due to the high probability of racemization, these reactions were not tried on a preparative scale. Hofmann degradation of the amide (*S*)-**14** proceeded under the same conditions as for the racemic compound[5] and for N^2-Z(Boc)-*L*-AsnOH,[7] and thus the 2,3-diaminopropionic acid fragment in the target compound (*S*)-**15** was created.

An attempt to synthesize (*S*)-**15** along a shorter route was made (Scheme 3). Curtius degradation of the azide which was generated from the acid (*S*)-**11** and *O*,*O*-diphenylphosphoryl azide (DPPA) in the presence of *t*BuOH led to the Boc-protected amino ester (*S*)-**16**. After purification by chromatography on silica gel, it was isolated in moderate



Scheme 3. Preparation of N^2-Z-N^2-Me-*L*-A_2pr [(*S*)-**15**] through Curtius degradation of (*S*)-**11**: (a) DPPA (1.1 equiv.), Et_3N (1 equiv.), *t*BuOH, 80 °C, 17 h; (b) TFA, 0 °C.



Scheme 4. Enantioselective synthesis of the heterocycle (*S*)-**1**: (a) 1.3 M aq. NaOH, Boc_2O, *t*BuOH; (b) HOBt, EDC, *N*,*N*-diisopropylethylamine (DIEA), CH_2Cl_2; (c) TFA, anisole, CH_2Cl_2, 20 °C; (d) Et_3N, AcOH (pH 8–9); (e) H_2, Pd/C, *N*,*N*-dimethylacetamide (DMAA).

yield and transformed directly to the amino acid (*S*)-**15** by simultaneous removal of both *tert*-butyl-containing protecting groups.

The optical purity of (*S*)-**15** obtained along this route was lower: it was necessary to recrystallize it twice from an EtOH/H_2O mixture in order to get an optical rotation value which was similar to that obtained earlier ($[\alpha]_D^{20}=-43.5$ versus −45.2 (Scheme 2), $c=1$, H_2O). Lower optical purity, higher losses during recrystallizations, the moderate yield of the intermediate (*S*)-**16**, and the necessity to purify it by column chromatography render this route inappropriate.

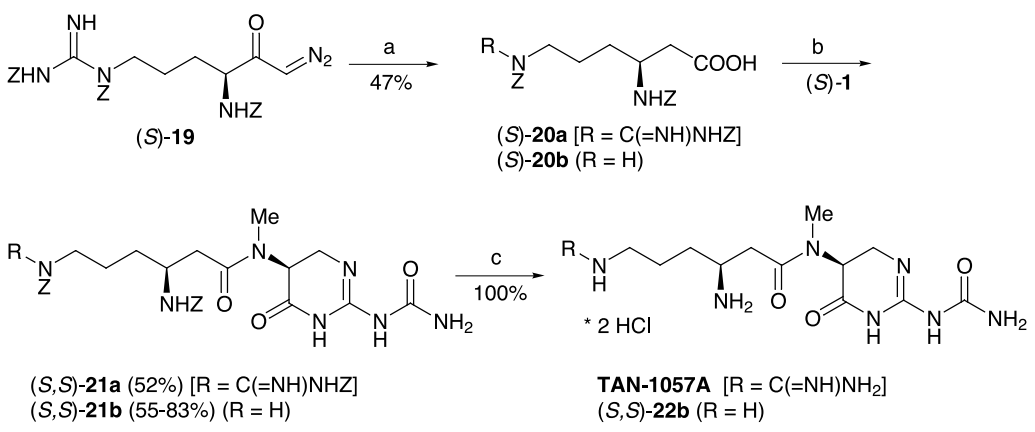
Surprisingly, esterification of (*S*)-**15** in methanol with thionyl chloride (HCl and $(MeO)_2SO$) was accompanied by considerable epimerization, and the e.e. of the amino ester (*S*)-**4** was found to be only 30–50%. Probably, the strongly electron-withdrawing properties of the protonated primary amino group enhance the α-CH acidity at the stereogenic center adjacent to the ester group (which may also be protonated in the strongly acidic medium), and therefore, rapid racemization occurs.[14]

Since the preparation of the amino ester (*S*)-**4** with high enantiomeric excess failed, the direct one-step cyclization as worked out for the preparation of the racemic heterocycle (*RS*)-**6** could not be used (Scheme 1). Therefore, a two-step cyclization was employed (Scheme 4, cf.[3]).

The monoprotected diamino acid (*S*)-**15** was first orthogonally bisprotected, and then coupled with easily available *S*-methylisothiobiuret hydroiodide (**5**) to give the intermediate (*S*)-**15**. In **8** the nitrogen next to the methylthio group turned out to be more nucleophilic than any of the other two, thus it is not necessary to use a protected equivalent of the compound **5**, as reported by Williams et al.[3] In monothiobiuret **5**, the nucleophilicity of the nitrogen atom next to the MeS-group proved to be much higher than that of the other two nitrogens, and the selectivity of the coupling was very high. Removal of the Boc-protecting group from the coupling product (*S*)-**18** followed by cyclization under very mild basic conditions afforded (*S*)-**6** (e.e.=92%). Hydrogenolysis under ordinary conditions gave the desired heterocycle (*S*)-**1** with an enantiomeric excess of 87%. This means that in the six synthetic steps the enantiomeric excess did decrease, but not drastically.

2.2. Diastereoselective synthesis of TAN-1057A as well as an analogue with lower acute toxicity

The last task to complete the synthesis of TAN-1057A was



Scheme 5. Diastereoselective synthesis of TAN-1057A*2HCl and its analogue with a β-lysine side chain: (a) hν, dioxane/water, 30 °C, 2 h; (b) HATU, DIEA, DMAA, 20 °C; (c) MeOH, H_2, $PdCl_2$, 25 °C.

to connect the (*S*)-tris-Z-β-homoarginine (**20a**) with the enantiomerically enriched heterocycle (*S*)-**1** (Scheme 5). Towards this goal, the tris-Z-protected diazoketone **19**,[5] precursor to **20a**, was irradiated with a daylight lamp in a dioxane/water mixture to yield the acid **20a** (47%).[15]

Several coupling reagents were tried. Treatment with EDC (alone or in the presence of HOBt or 7-aza-1-hydroxybenzotriazole) failed to give the coupling product (*S*,*S*)-**21a**. The desired compound was prepared in high crude yield (84%) by using of 2 equiv. of HATU and DIEA. The coupling reaction was not accompanied by any detectable epimerization: the diastereomeric ratio of TAN-1057A/B in the crude product was about 93:7, virtually the same as the enantiomeric ratio of the starting heterocycle (*S*)-**1** with an e.e.=87%. The minor epimer was removed completely by recrystallization from dichloromethane. However, recrystallization was accompanied by considerable losses, so that the isolated yield of the pure A-diastereomer dropped to 52% from about 79% calculated from the crude yield of the 93:7 mixture. The purity of the recrystallized coupling product (*S*,*S*)-**21a** was confirmed by LC–MS and the elemental analysis.

Compound (*S*,*S*)-**21a** exists as a mixture of two amide rotamers which (in [D_6]DMSO) display two singlets of *N*-methyl groups in the ^{1}H NMR spectrum (600 MHz): a low-field broad resonance with higher intensity at 2.85 ppm, and another (sharp) resonance at 2.66 ppm. The 1:1 epimeric mixture (C-5) of the coupling product **21a** prepared from the racemic heterocycle (*RS*)-**1**[5] shows three singlets of *N*-methyl groups in the ^{1}H NMR spectrum: a low field resonance (2.85 ppm) and two closely positioned sharp singlets with δ=2.65 and 2.66 ppm. Each of them is ca. two times less intensive than the high-field singlet (2.66 ppm) for the A-diastereomer. Therefore, the degree of diastereomeric purity may easily be estimated by ^{1}H NMR spectroscopy. An attempted separation of **21a** by HPLC failed.

The final deprotection of (*S*,*S*)-**21a** by catalytic hydrogenation with $PdCl_2$ as a (pre)catalyst and a source of HCl necessary for the salt formation, was also found to occur without epimerization. The CD-spectrum of this sample was identical to that of HPLC-purified TAN-1057A reported earlier.[2] This rigorously proves the assignment of the absolute configuration at C-5 initially made by the Takeda group.[2] The absolute value of the optical rotation of pure TAN-1057A*2HCl found here is lower than that previously reported ($[\alpha]_D^{22}=-22.7$ versus -39.1,[2] c=0.53, H_2O).[16] However, this lower value cannot be explained with epimerization, though the B-epimer has $[\alpha]_D^{22}=+72.6$ (c=0.53, H_2O).[2] The diastereomeric purity of this current sample was established unequivocally by comparison of its ^{1}H NMR spectrum (600 MHz) with that of the epimeric mixture. There is a striking contrast between them. The synthetic sample has one set of signals; only the *N*-methyl group displays two sharp singlets of the two rotamers: at 3.12 ppm and a much less intensive one at 2.88 ppm. In the case of the epimeric mixture of TAN-1057A,B, nearly all the signals are doubled. The most convenient way to estimate the diastereomeric purity is by measuring the relative intensities of the two resolved singlets of the *N*-methyl group (near 3.1 ppm), as there is one signal for each epimer.

As has been reported previously,[4b–e] several novel analogues of TAN-1057A,B showed lower acute toxicity compared to the natural product, yet with concomitant retention of excellent anti-microbial activity. For example, the analogue of the compound (*S*,*S*)-**22b** (Scheme 5) first prepared from the racemic heterocycle (*RS*)-**6** and bis-Z-β-(*S*)-lysine (**20b**) as a 1:1 mixture of two diastereomers was shown to be at least 4 times less toxic than TAN-1057A/B (mice, i. p.), while in vivo anti-staphylococcal activity was nearly the same.[4b,d] Therefore the pure diastereomer (3′*S*,5*S*)-**21b** was synthesized by coupling the enantiomerically enriched heterocycle (*S*)-**1** (e.e.=75–87%) with bis-Z-β-(*S*)-lysine (**20b**). After recrystallization, the obtained product **21b** (55% yield) had de=85–90%. Final deprotection of (*S*,*S*)-**21b** was performed under the same conditions as for TAN-1057A. The CD-spectrum of (3′*S*,5*S*)-**22b** is very similar to that of TAN-1057A. The diastereomeric purity of this sample was also confirmed by ^{1}H NMR spectroscopy. As for TAN-1057A, there is only one set of signals including well-resolved sharp singlets of the *N*-Me group at 3.16 and 2.89 ppm (the latter is much less intense and indicates the presence of a small amount of the second amide rotamer).

3. Conclusion

The first synthesis of the chiral heterocycle of TAN-1057A with high enantiomeric purity has been accomplished. The overall yield was about 9% over 14 steps, starting from *L*-aspartic acid. The same methodology is in principle applicable for the synthesis of the (*R*)-enantiomer (*R*)-**1**. Starting from (*S*)-**1**, diastereomerically pure TAN-1057A was synthesized (5% yield over 16 steps), and thus the absolute configurations at C-5 in both natural diastereomers of TAN-1057 were rigorously confirmed. No chromatographic separations were necessary, therefore these synthetic procedures may easily be scaled-up. In addition, the route to numerous analogues with various side-chains is feasible (for example, compound (*S*,*S*)-**22b**). Enantiomerically pure orthogonally protected (*S*)-N^2-methyl-2,3-diaminopropionic acid (*S*)-**17** also is a valuable intermediate for the synthesis of other biologically active compounds.[17]

4. Experimental

4.1. General

Melting points (uncorrected) were determined in capillaries using a Büchi 510 apparatus. IR: Bruker IFS 66 (FT-IR) spectrometer, measured as KBr pellets. ^{1}H NMR: Bruker AM 250 instrument (250 MHz), and VARIAN INOVA-600 spectrometer (600 MHz); ^{13}C (and DEPT) NMR: Bruker AM 250 at 62.9 MHz and Varian UNITY 300 at 75.5 MHz. All spectra are calibrated against tetramethylsilane as an internal standard (δ=0) or the signals of residual protons of deuterated solvents: 7.26 for $CHCl_3$, 2.50 for [D_5]DMSO and 3.30 for [D_3]MeOH. Multiplicities of signals are reported as follows: s=singlet, d=doublet, t=triplet,

q=quartet, quint=quintet, m_c=centrosymmetrical multiplet. Coupling constants (*J*) are given in Hz. EI-MS: Finnigan MAT 95 and Varian CH 5 spectrometers (70 eV). HPLC-MS: Hewlett–Packard 1100 instrument (Micromass Platform LCZ). HRMS: Micromass LCT (TOF MS, electrospray ionization, positive and negative modes). HPLC-MS parameters: column: Kromasil C 18; 50×2.1 mm; eluent A: 5 mL 70% $HClO_4$ in 1 L H_2O; eluent B. MeCN; 0–0.5 min: 98% A+2% B, 0.5–4.5 min: 2–90% B, 4.5–6.5 min: 10% A+90% B; UV-detection at 210 nm; column temp. 30 °C, flow rate 0.75 mL/min. Analytical TLC: Macherey-Nagel ready-to-use plates AluGram Sil G/UV_{254}. Detection under a UV-lamp at 254 nm, development with molybdatophosphoric acid solution (5% in EtOH) or 0.5% aq. $KMnO_4$. Column chromatography: Merck silica gel, grade 60, 230–400 mesh. Optical rotations were measured with a Perkin–Elmer polarimeter, and CD-spectra were recorded with a *J*-810 instrument (JASCO). Elemental analyses were performed by the Mikroanalytisches Laboratorium des Instituts für Organische und Biomolekulare Chemie der Georg-August Universität Göttingen. Solvents were purified according to standard procedures. Organic solutions were dried over $MgSO_4$. All reactions were carried out with magnetic stirring, unless otherwise stated.

4.1.1. *L*-Aspartic acid 3-methyl ester [(*S*)-7] and *N*-benzyloxycarbonyl-*L*-asparaginic acid 3-methyl ester [(*S*)-8]. The title compounds were prepared as described in the literature.[8] Unlike the authors of the original publication, we were not able to obtain a crystalline sample of (*S*)-**8** (reported mp 98 °C). Diester (*S*)-**9** was synthesized as reported,[9] $[\alpha]_D^{20}=-2.3$ (*c* 1.75, EtOAc); lit.:[9] $[\alpha]_D^{20}=-1.7$ (*c* 1.75, EtOAc). In the latter publication compound (*S*)-**8** is also described to be a colorless oil. The isothiuronium salt **5** was synthesized according to the known procedure.[18] Bis-Z-β-(*S*)-lysine **20b** was purchased from EMKA Chemical Enterprise, Ltd.

4.1.2. 1-*tert*-Butyl methyl (*S*)-*N*-benzyloxycarbonyl-*N*-methylaspartate (*N*-Z-*N*-MeAsp(OMe)O*t*Bu, (*S*)-10). To a solution of diester (*S*)-**9** (21.4 g, 63.4 mmol) and MeI (28.0 mL, 63.6 g, 448 mmol) in anhydrous DMF (100 mL), was added 15.0 g (64.7 mmol) of Ag_2O, and the black suspension was vigorously stirred at room temperature for 7 h. A small amount of the reaction mixture was worked-up (see below) and analyzed by means of TLC (eluent EtOAc/hexane, 1:4) or, better, NMR spectroscopy to determine, whether the reaction was complete; compound (*S*)-**9**: R_f=0.53; compound (*S*)-**10**: R_f=0.57. Dichloromethane (700 mL) was added to the reaction mixture, and it was filtered through Celite®. The filter cake was washed with dichloromethane (2×100 mL), and the combined organic solutions were washed with saturated aq. $Na_2S_2O_3$ or 10% aq. NaCN solution (2×100 mL) and water (8×100 mL). After drying, they were concentrated in vacuo, and the oily residue was kept at 0.01 mm Hg to remove traces of DMF, and compound (*S*)-**10** was isolated as a yellowish oil (21.8 g, 98%) and was used in the next step without further purification. ^{1}H NMR ($CDCl_3$, the signals of the major rotamer are marked with ∗) δ 1.35/1.40∗ (s, 9H), 2.63–2.80 (m, 1H, C*H*H), 2.93/2.94∗ (s, 3H, *N*Me), 2.91–3.10 (m, 1H, CH*H*), 3.64/3.66∗ (s, 3H, OMe), 4.75 (m_c, 1H, CH), 5.03–5.25 (m, 2H, OCH_2), 7.28 (br. s, 5H); ^{13}C NMR (62.9 MHz, $CDCl_3$, the signals of the major rotamer are marked with ∗) δ 27.7∗/27.8 (Me), 33.5/34.4∗ (*N*Me), 34.9∗/36.3 (CH_2), 51.7∗/51.8 (OMe), 57.6/58.2∗ (CHN), 67.1/67.4∗ (OCH_2), 81.9∗/82.1 (C–O), 127.7 (CH), 127.9 (CH), 128.3 (CH), 136.5 (C), 156.01/156.07∗ (NC=O), 168.85∗/168.91 (C=O), 171.1/171.3∗ (C=O).

4.1.3. 1-*tert*-Butyl (*S*)-*N*-benzyloxycarbonyl-*N*-methylaspartate (*N*-Z-*N*-MeAspO*t*Bu, (*S*)-11). To a solution of diester (*S*)-**10** (102 g, 0.29 mol) in MeOH (0.8 L) kept in an ice-bath, was added dropwise within 4 h a solution of $LiOH^*H_2O$ (12.2 g, 0.29 mol) in water (200 mL). The mixture was left to warm up to room temperature. Most of the MeOH was evaporated in vacuo (bath temp. ≤35 °C), the residue was diluted with water (0.5 L) and extracted with ether (3×150 mL). The aqueous layer was acidified with cold 6 M HCl up to pH 3–4, and extracted with ether (3×200 mL). The organic layers were washed with brine, dried and evaporated to give 75.9 g (78%) of (*S*)-**11** as an oil. ^{1}H NMR ($CDCl_3$, the signals of the major rotamer are marked with ∗) δ 1.34/1.40∗ (s, 9H), 2.66–2.89 (m, 1H, C*H*H), 2.96 (s, 3H, *N*Me), 3.00–3.17 (m, 1H, CH*H*), 4.71 (q, 1H, *J*=6.6 Hz, CH), 5.04–5.21 (m, 2H, OCH_2), 7.31–7.39 (m, 5H), ~9.9 (br. s, 1H, COOH); ^{13}C NMR (62.9 MHz, $CDCl_3$, the signals of the major rotamer are marked with ∗) δ 27.7 (Me), 33.7 (*N*Me), 34.4∗/34.9 (CH_2), 57.5/58.2∗ (CHN), 67.4∗/67.6 (OCH_2), 82.3∗/82.4 (C–O), 127.7 (CH), 127.9 (CH), 128.5 (CH), 130.4/136.4∗ (C), 155.9/156.3∗ (NC=O), 168.7/168.8∗ (C=O), 176.2/176.5∗ (C=O).

4.1.4. (*S*)-3-*tert*-Butoxycarbonyl-3-[(*N*-benzyloxycarbonyl-*N*-methyl)amino]propanoylsuccinimide (*N*-Z-*N*-MeAsp(OSu)O*t*Bu, (*S*)-12). To a solution of the ester (*S*)-**11** (8.94 g, 26.5 mmol) in EtOAc (50 mL) was added at +5 °C *N*-hydroxysuccinimide (3.35 g, 29.2 mmol) and then dropwise with ice-cooling a solution of *N*,*N*′-dicyclohexylcarbodiimide (6.00 g, 29.1 mmol) in 50 mL of dioxane. The reaction mixture was kept overnight at +5 °C. *N*,*N*-Dicyclohexylurea was removed by filtration, washed with dioxane (15 mL), and the filtrate was concentrated in vacuo to give 11.2 g (97%) of (*S*)-**12** as a solid. An analytical sample was recrystallized from dioxane–ether, mp 120–122 °C. Found C 57.81, H 6.19; calcd for $C_{21}H_{26}N_2O_8$ (434.43) C 58.06, H 6.03; ^{1}H NMR ($CDCl_3$, the signals of the major isomer are marked with ∗) δ 1.37/1.41∗ (s, 9H, Me), 2.81 (br. s, 3H, *N*Me), 3.00 (s, 4H, CH_2), 2.91–3.41 (m, 2H, CH_2), 4.61–4.75 (m, 1H, CH), 5.02–5.28 (m, 2H, CH_2O), 7.30–7.39 (m, 5H); ^{13}C NMR (62.9 MHz, $CDCl_3$, the signals of the major isomer are marked with ∗) δ 25.5 (CH_2), 27.7 (Me), 31.7∗/32.2 (CH_2), 34.2/34.4∗ (Me*N*), 57.5/58.3∗ (CHN), 67.4∗/67.6 (CH_2O), 82.7∗/82.9 (C–O), 127.8 (CH), 127.9 (CH), 128.4 (CH), 136.4 (C), 155.6/156.1∗ (NCO), 166.2/166.6∗ (CO), 167.9/168.0∗ (CO), 168.7/168.8∗ (CO).

4.1.5. N^2-Benzyloxycarbonyl-N^2-methyl-*L*-asparagine *tert*-butyl ester (N^2-Z-N^2-Me-*L*-AsnO*t*Bu, (*S*)-13). To a suspension of compound (*S*)-**12** (11.05 g, 25.4 mmol) in THF (100 mL) was added dropwise at 0 °C 4 mL of 25% aq. NH_3. The reaction mixture was stirred at room temperature overnight, filtered, and the filtrate was evaporated in vacuo.

The residue was dissolved in ether (200 mL), the solution was washed with 0.5 M aq. HCl (20 mL), H_2O (20 mL), sat. aq. $NaHCO_3$ (20 mL) and brine (20 mL). After drying and evaporation of the solvent, 7.15 g (84%) of the title compound was obtained as an oil which was used in the next step without further purification. ^1H NMR ($CDCl_3$, the signals of the major rotamer are marked with ∗) δ 1.38 (s, 9H, Me), 2.48–3.04 (m, CH_2), 2.96/2.99* (s, *N*Me, total intensity 5H), 4.49* (dd, J=5.8, 8.4 Hz, CH) and 4.68 (t, J=7.1 Hz, total intensity 1H, CH), 4.98–5.23 (m, 2H, CH_2O), 5.82/5.93*/6.00/6.22* (br. s, total intensity 2H, NH_2), 7.38 (br. s, 5H); ^{13}C NMR (62.9 MHz, $CDCl_3$, the signals of the major isomer are marked with ∗) δ 27.8 (Me), 34.7*/35.2 (CH_2), 36.0*/36.5 (Me*N*), 58.3/59.5* (CHN), 67.2*/67.4 (CH_2O), 82.0*/82.8 (C–O), 127.7 (CH), 128.0 (CH), 128.5 (CH), 136.4 (C), 156.4 (NCO), 169.4 (CO), 172.7 (CO).

4.1.6. N^2-Benzyloxycarbonyl-N^2-methyl-*L*-asparagine (N^2-Z-N^2-Me-*L*-AsnOH, (*S*)-14). To a solution of N^2-Z-N^2-Me-*L*-AsnO*t*Bu (16.0 g, 47.6 mmol) in CH_2Cl_2 (20 mL) was added dropwise at 0 °C TFA (30 mL), and the solution was stirred at room temperature for 4 h. Volatiles were evaporated in vacuo, the residue was triturated with anhydrous ether (200 mL) and kept at 0 °C overnight, until it solidified completely. After washing with anhydrous ether (3×100 mL) and drying in vacuo, 11.0 g of a colorless solid was obtained; $[\alpha]_D^{20}=-47.0$ (c 0.99, MeOH), e.e.= 77% (HPLC on a chiral stationary phase: poly(*N*-acyloyl-*L*-leucid-*d*-methylamide) grafted silica gel; column 250×20 mm, isohexane/THF=3:7, 1 mL/min; (*S*)-isomer: 7.75 min, (*R*)-isomer: 9.77 min). The solid was powdered and stirred in 2-propanol (100 mL) at 50–60 °C for 30 min with occasional sonification. The suspension was left overnight at room temperature and filtered through a sintered glass filter (No. 4). The filter cake was washed with EtOAc (20 mL), and the clear solution was evaporated in vacuo. The residue was recrystallized from 2-propanol and EtOAc mixture, and the solid which formed was collected by filtration to give 7.71 g (58%) of the title compound with $[\alpha]_D^{20}=-59.2$ (c 0.95, MeOH), e.e. ≥99%, mp 129 °C (dec.). An analytical sample was recrystallized once more from 2-propanol. Found C 56.08, H 5.75, N 9.84; calcd for $C_{13}H_{16}N_2O_5$ (280.27): C 55.71, H 5.75, N 9.99; $[\alpha]_D^{20}=-60.9$ (c 1.0, MeOH); lit.:[11a] $[\alpha]_D^{20}=-60.8$ (c 1.0, MeOH), mp 134–136 °C. The other spectra of (*S*)-**18** are identical to those of the racemate[5] and to the previously published ones.[11a]

4.1.7. (*S*)-3-Amino-2-(*N*-benzyloxycarbonyl-*N*-methyl)-aminopropionic acid (N^2-Z-N^2-Me-*L*-A_2pr, (*S*)-15). The title compound was prepared in 75% yield from (*S*)-**14** as described for the racemate (*RS*)-**14**;[5] $[\alpha]_D^{20}=-45.2$ (c 1.05, water), mp 204 °C (dec., aq. EtOH). Found C 57.43, H 6.40, N 10.95; calcd for $C_{12}H_{16}N_2O_4$ (252.26) C 57.13, H 6.39, N 11.10. The spectra of (*S*)-**14** were identical to those of the racemate.[5]

4.1.8. *tert*-Butyl(*S*)-2-(*N*-benzyloxycarbonyl-*N*-methyl)-amino-3-(*tert*-butoxycarbonyl)amino-propionate (N^2-Z-N^2-Me-N^3-Boc-*L*-A_2pr*O*t*Bu, (*S*)-16). To a solution of compound **11** (1.69 g, 5.01 mmol) and Et_3N (0.51 g, 5.0 mmol) in 20 mL of anhydrous *t*BuOH was added under nitrogen DPPA (1.19 mL, 5.50 mmol). The reaction mixture was stirred at 80 °C for 17 h, diluted with ethyl acetate (200 mL), washed with 1% aq. solution of citric acid (30 mL), sat. aq. $NaHCO_3$ (50 mL), dried and evaporated. Chromatography on SiO_2 (60 g) eluting with an EtOAc/hexane mixture (1:4) gave 1.00 g (49%) of (*S*)-**16** as a colorless oil; R_f=0.75 (CH_2Cl_2/MeOH, 20:1). ^1H NMR ($CDCl_3$, the signals of the major rotamer are marked with ∗) δ 1.40 (s, 18H, 2×*t*Bu), 2.92 (s, 3H, *N*Me), 3.37/3.58* (m, 2H, CH_2), 4.42 (m, 1H, CH), 4.79/4.83* (m, 1H, NH), 5.00–5.23 (m, 2H, CH_2O), 7.29–7.35 (m, 5H); ^{13}C NMR (62.9 MHz, $CDCl_3$, the signals of the major rotamer are marked with ∗) δ 27.8 (Me), 28.2 (Me), 32.9*/33.2 (*N*Me), 39.2*/39.5 (CH_2), 59.9/60.4* (CH), 67.2*/67.4 (CH_2O), 79.3*/79.5 (CO), 82.0*/82.1 (CO), 127.6 (CH), 127.7 (CH), 128.4 (CH), 136.1 (C), 136.5 (C),155.8 (C), 155.9 (C), 156.2 (C), 157.0 (C), 168.7 (CO).

4.1.9. Reaction of compound (*S*)-16 with trifluoroacetic acid. A solution of (*S*)-**16** (1.00 g, 2.45 mmol) in TFA (5 mL) prepared at 0 °C, was stirred at room temperature for 1.5 h. Volatiles were evaporated in vacuo at room temperature, the residue was dissolved in water (10 mL), and 25% aq. NH_3 was added carefully until the pH value reached 7. The suspension was evaporated to dryness, and the solid residue was recrystallized from EtOH to give 0.423 g (68%) of (*S*)-**15** with $[\alpha]_D^{20}=-38.8$ (c 0.98, H_2O). In another run the $[\alpha]_D^{20}$ was found to be −40.2° (c 0.99, H_2O). A second recrystallization from aq. EtOH afforded 0.280 g (45%) of (*S*)-**19** with $[\alpha]_D^{20}=-43.5°$ (c 1.00, H_2O).

4.1.10. Methyl (−)-3-amino-2-(*N*-benzyloxycarbonyl-*N*-methyl)aminopropionate hydrochloride [(*S*)-4]. The title compound was prepared from 0.475 g (1.88 mmol) of (*S*)-**15** in anhydrous MeOH (5.6 mL) in the presence of 0.49 mL $SOCl_2$ as described before.[5] The reaction mixture was stirred at room temperature for 1.5 h and kept at +5 °C overnight. Crystallization from MeOH (5 mL) and ether (20 mL) gave 0.490 g of (*S*)-**4** (86%) with mp 171–172 °C (the racemate has mp 175–176 °C[5]) and $[\alpha]_D^{20}=-51.8$ (c 0.92, MeOH); e.e.≈55%. HPLC on Gromchiral AD; heptane/EtOH/TFA, 82:17:0.2, 0.2 mL/min; column 250×2 mm, R_t=11.82 min (*S*-isomer) and 14.87 min (*R*-isomer). The spectral data were found to be identical to these of the racemic compound.[5]

4.1.11. (*S*)-2-(*N*-Benzyloxycarbonyl-*N*-methyl)amino-3-(*tert*-butoxycarbonylamino)propionic acid [(*S*)-17, N^2-Z-N^2-Me-N^3-Boc-*L*-A_2pr].[19] A suspension of (*S*)-**15** (0.660 g, 2.62 mmol) in 10 mL of water was cooled to 0 °C, and 2.0 mL of 1.3 M aq. NaOH was added dropwise followed by *t*BuOH (5 mL) and Boc_2O (0.661 g, 3.02 mmol). The cold bath was removed, and stirring was continued at room temperature. Gas evolution started after about 15 min, and the pH value gradually decreased. It was kept at about 9 by careful addition of sat. aq. Na_2CO_3 solution. The reaction was complete within 3.5 h. The reaction mixture was diluted with H_2O (20 mL), extracted with hexane (2×20 mL), and acidified at +5 °C with 5% aq. $KHSO_4$ (pH ≈2). Then it was extracted with ether (4×20 mL); the combined ether layers were washed with brine, dried, and evaporated to yield 0.90 g (97%) of (*S*)-**17** as a glass-like foam. The racemate (*RS*)-**17** was obtained

analogously from (*RS*)-**15**[5] and had mp 133–134 °C (EtOAc/PE). IR: ν=3384, 3328, 2940, 2863, 1690, 1634, 1540, 1518, 1450, 1382, 1363, 1319, 1271, 1169 cm^{-1}; ^1H NMR ($CDCl_3$, signals of the major isomer are marked with *) δ 1.41* s/1.44 br. s ($\sum$ 9H, *t*Bu), 2.91/2.94* (s, $\sum$ 3H, Me*N*), 3.40 br. m/3.62* m ($\sum$ 2H, CH_2N), 4.48* t/4.60 br. m ($\sum$ 1H, CHN), 4.89/5.02* (br. t, $\sum$ 0.5H, NHCO), 5.12 br. s/5.16* s ($\sum$ 2H, CH_2O), 6.16*/6.23 (br. s, $\sum$ 0.5H, NHCO), 7.23–7.39 m (5H), 9.63 br. s (1H, COOH); ^{13}C NMR (62.9 MHz, $CDCl_3$, signals of the major isomer are marked with *) δ 28.3 (Me in *t*Bu), 33.1/33.4* (Me*N*), 39.2/39.5* (CH_2N), 59.6/60.1* (CHN), 61.7*/67.8 (CH_2O), 79.8 (C–O), 127.7, 127.9, 128.1, 128.5 (CH), 136.0/136.1* (C), 156.0, 156.9 (CONMe), 172.8 (COOH); ESI-MS (positive mode), *m/z* (rel. int., %) 727 (100) [2M+Na^+], 375 (24) [M+Na^+]. (*S*)-**17***DCHA salt was prepared from (*S*)-**17** and dicyclohexylamine in EtOAc and precipitated at +5 °C by addition of hexane; mp 120–121 °C; found C 64.98, H 8.76, N 7.61; calcd for $C_{29}H_{47}N_3O_6$ (533.71) C 65.26, H 8.88, N 7.87; $[\alpha]_D^{27}$=−3.9 (*c* 1.24, $CHCl_3$).

4.1.12. (*S*)-5-(*N*-Benzyloxycarbonyl-*N*-methyl)amino-3,4,5,6-tetrahydro-2-ureidopyrimidin-4-one [(*S*)-6]. *Coupling product* **18**. To a suspension of (*S*)-**17** (0.900 g, 2.55 mmol) in CH_2Cl_2 (15 mL), was added *N*-hydroxybenzotriazole hydrate (0.430 g, 2.81 mmol), and the mixture was cooled to 0 °C. EDC (0.434 g, 490 μL, 3.16 mmol) was added dropwise, and the precipitate disappeared. Stirring was continued for 20 min at 0 °C, DIEA (645 mg, 825 μL, 4.99 mmol) was added dropwise followed by the compound **5** (1.30 g, 4.98 mmol). Stirring at 0 °C was continued for 15 min, and the clear solution was kept at +5 °C overnight. Then, CH_2Cl_2 (200 mL) was added, and the solution was washed with water (20 mL), 5% aq. $KHSO_4$ (20 mL), water (20 mL), 1% aq. $NaHCO_3$ (20 mL), and brine (20 mL). After drying and evaporation of the solvent, a semi-crystalline mass of the crude coupling product **18** was obtained (1.19 g, quantitative yield); R_f~0.5 (CH_2Cl_2/MeOH, 20:1, UV-active spot). $[\alpha]_D^{20}$=−17.0 (*c* 1.14, $CHCl_3$); IR: ν=3353, 2978, 1700, 1570, 1456, 1400, 1366, 1230, 1165, 1008 cm^{-1}; ^1H NMR ($CDCl_3$, signals of the major isomer are marked with *) δ 1.39 (s, 9H, *t*Bu), 2.28/2.32* (s, $\sum$ 3H, Me*N*), 3.01 (s, 3H, Me*S*), 3.43/3.65* (m, 2H, CH_2N), 4.40 (br. t, 1H, CHN or NH), 4.57 (br. t, 1H, NH or CHN), 4.98 (m, 2H, NH_2), 5.08/5.20* (m, 2H, CH_2O), 5.42*/5.58 (br. s, 1H, NH), 7.32–7.39 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$, the signals of the major isomer are marked with *) δ 14.3 (*S*Me), 28.26*/28.32 (Me), 33.2*/34.1 (br. Me*N*), 38.8*/39.2*/39.7 (br. *N*CH_2), 61.4*/63.3 (br. CHN), 67.2/67.9*/68.0* (br. CH_2O), 79.7/79.8 (br. C–O), 127.84, 127.9, 128.0, 128.2, 128.5*, 128.8 (CH), 135.8/136.2* (C), 155.5/155.7*, 156.8 (NCO), 163.3, 168.2/168.6/169.2* (CO). ESI-MS (positive mode), *m/z* (rel. int., %) 957 (100) [2M+Na^+], 490 (29) [M+Na^+].

*Deprotection and cyclization of the coupling product **18** to (S)-**6***

To a suspension of the semi-solid **18** (1.18 g, 2.55 mmol) in anisole (5 mL), was added at room temperature a mixture of CH_2Cl_2 (10 mL) and TFA (7.5 mL), and the solution was stirred for 2.5 h. When the deprotection reaction was complete (TLC), the solvents were evaporated in vacuo (0.1 mm Hg) at room temperature, the residue was triturated with anhydrous ether (2×15 mL, with decantation) and dried in vacuo (0.01 Torr). Then it was suspended in CH_2Cl_2, and Et_3N (399 mg, 550 μL, 3.95 mmol) was added at 0 °C. Slow gas evolution was observed, and a precipitate started to form. A sheet of wet indicator paper introduced into the head space of the reaction flask indicated that the pH was about 11. A few small drops of glacial AcOH were added, until the pH value (measured in the same way) reached 8–9. Stirring at room temperature was continued overnight. The solvent was evaporated in vacuo, 10 mL of water was added, and the suspension was sonificated in an ultra-sound bath (30 s). The precipitate was removed by filtration, washed with H_2O (10 mL), cold MeOH (2×5 mL), ether (5 mL), and dried in vacuo to give 447 mg (55%) of (*S*)-**6**, $[\alpha]_D^{20}$=−175 (*c* 0.525, DMF), e.e.=92%; column: Chiralpak AS (250×4.6 mm), eluent: heptane/ethanol (1:1), 1 mL/min; (*R*)-isomer: 6.82 min, (*S*)-isomer: 8.78 min. The spectral data were identical to those of the racemate.[5] In another run a product with $[\alpha]_D^{20}$=−157 (*c* 0.545, DMF) was obtained in 65% yield. A sample of this product (464 mg) was suspended in 15 mL of DMAA with sonification and warming at 30 °C. The insoluble fraction was removed by filtration (35 mg after washing with ether and drying), and the solution was used in the next step (see below). (*S*)-**1** was obtained with practically the same e.e. (86%). This simple way to increase the e.e. is based on the fact that the solubility of the racemate (*RS*)-**6** is much lower than that of (*S*)-**6**.

4.1.13. (*S*)-3,4,5,6-Tetrahydro-5-methylamino-2-ureidopyrimidin-4-one [(*S*)-1]. To a solution of (*S*)-**6** (360 mg, 1.62 mmol, e.e.=92%) in 15 mL of anhydrous *N*,*N*-dimethylacetamide (DMAA) was added 200 mg of 10% Pd/C. (Merck, oxidized form). The reaction mixture was flushed with N_2, then with hydrogen, and stirred at room temperature. A rapid consumption of H_2 (from a balloon attached to the reaction flask) was observed. After 1.5 h, the reaction was complete (detection by TLC (CH_2Cl_2/MeOH, 1:1); R_f of (*S*)-**6**~0.9, R_f of (*S*)-**1**~0.5). The suspension was filtered through Celite®, the filter cake was washed with DMAA (3×3 mL), and the filtrate was evaporated in vacuo (bath temp. 30–40 °C, 0.01 mm Hg). The residue was triturated with anhydrous ether (10 mL), the solid residue was filtered off, washed with anhydrous ether (10 mL), and dried to give 200 mg (96%) of (*S*)-**1**, $[\alpha]_D^{20}$=−247 (*c* 0.635, DMF), e.e.=87%; column: Chiral AS (250×2 mm); heptane/EtOH/Et_2NH, 65:34.8:0.2; 0.25 mL/min; (*S*)-isomer: 6.63 min, (*R*)-isomer: 8.78 min.

4.1.14. (*S*)-N^{β},N^{ε},N^{ω}-Tris(benzyloxycarbonyl)-β-homoarginine [(*S*)-20a].[15] To a solution of the diazoketone (*S*)-**19** (22.2 g, 37.0 mmol) in 250 mL of dioxane was added 18 mL of water. The solution was cooled in an ice bath and irradiated for 2 h with a 300 W daylight lamp (the internal temp. was about 30 °C). The solvents were removed in vacuo, and the semi-solid residue was crystallized from acetone/ether mixture to give a first crop (5.6 g) as a colorless solid. The mother liquors were concentrated, and the residue was purified by passing it through a short silica gel pad (100 g) eluting with a gradient of CH_2Cl_2/EtOAc (1:1) to CH_2Cl_2/EtOAc/MeOH (8:8:1). After evaporation, the main fraction was crystallized from acetone/ether

yielding another 4.6 g of the title compound, total yield 10.2 g (47%). An analytical sample was recrystallized once more from EtOH. Found C 62.28, H 6.29; calcd for $C_{31}H_{34}N_4O_8^*1/2H_2O$ (599.62) C 62.09, H 5.88; $[\alpha]_D^{20}=+0.8$ (*c* 1.21, $CHCl_3$); lit.[20] $[\alpha]_D^{20}=-2.5$ (*c* 1.1, CH_2Cl_2/MeOH); 30.4 (CH_2), ^{1}H NMR ($CDCl_3$) δ 1.42–1.65 (m, 4H, H-4 and H-5), 2.55 (m, 2H, H-2), 3.88 (m, 3H, H-3 and H-6), 5.05 s, 5.17s and 5.25 s (6H, $PhCH_2O$), 5.58 (d, *J*=5 Hz, 1H, NH), 7.34–7.39 (m, 15H), 9.27 and 9.41 (br. s, 2H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 25.3 (CH_2), 30.4 (CH_2), 38.7 (CH_2), 44.3 (CH_2), 47.7 (CH), 66.6, 67.0 68.9 (CH_2O), 127.8, 127.88, 127.94, 128.02, 128.11, 128.35, 128.4, 128.77, 128.82 (CH), 134.6, 136.4, 136.8 (C), 155.8, 156.0 (NCO), 160.5, 163.7 (CO), 175.9 (br. COOH); ESI-MS (positive mode), *m*/*z* (rel. int., %) 1203 (64) [2M+Na^+], 613 (39) [M+Na^+], 591 (39) [M+H^+]; (negative mode), 1201 (34) [2M−2H+Na^+], 589 (100) [M−H^+].

4.1.15. (3′*S*,5*S*)-5-[*N*-Methyl-*N*-[*N*$^{\beta}$,*N*$^{\varepsilon}$,*N*$^{\omega}$-tris(benzyloxycarbonyl)-β-homoarginyl]amino]-5,6-dihydro-2-ureidopyrimidin-4(1*H*)-one [(*S*,*S*)-21a]. To a suspension of the acid (*S*)-**20a** (495 mg, 0.84 mmol) and (*S*)-**1** (155 mg, 0.84 mmol) in anhydrous DMAA (4 mL) was added HATU (646 mg, 1.70 mmol) in one portion at room temperature followed by DIEA (0.29 mL, 227 mg, 1.75 mmol) which was added dropwise without external cooling. A slightly exothermic reaction was observed, and the solid heterocycle (*S*)-**1** gradually dissolved. After 4.5 h at room temperature, the solvent was evaporated in vacuo (0.01 mm Hg, bath temp. 30–40 °C), and the residue was dissolved in dichloromethane (50 mL). The solution was washed with water, 5% aq. $KHSO_4$, water, sat aq. $NaHCO_3$, brine (10 mL each), and dried. The solvent was evaporated, and the semi-solid residue was triturated with 10 mL of a mixture of EtOAc and ether (1:1). After keeping this suspension overnight at +5 °C, the solid crude coupling product (*S*,*S*)-**21a** was collected on a filter and washed with ether (10 mL). After drying, the crude product (0.53 g, 84% yield) was recrystallized from dichloromethane (45 mL). The fraction, which was insoluble in boiling dichloromethane, was removed by filtration (0.10 g after drying), the filtrate was diluted with EtOAc (1:1), and kept at +5 °C overnight. The colorless solid of (*S*,*S*)-**21a** (0.33 g, 52%) was collected, washed on a filter with ether (10 mL) and dried in vacuo (0.01 Torr). Found C 58.16, H 5.81, N 16.28; calcd for $C_{37}H_{43}N_9O_9^*1/4H_2O$ (761.8) C 58.30, H 5.75, N 16.54; $[\alpha]_D^{20}=-51$ (*c* 0.26, DMF); HPLC-MS: R_t=4.52 min (peak area 100%); IR: ν=3388, 3266, 3133, 2946, 1718, 1610, 1575, 1507, 1456, 1377, 1257, 1097, 1029 cm^{-1}; ^{1}H NMR ([D_6]DMSO, 600 MHz, signals of the major rotamer are marked with ∗) δ 1.32, 1.42, 1.51 and 1.58 (4 m, 4H, H-4′ and H-5′), 2.22 (dd, *J*=16.2, 6.6 Hz, A-part of an AB-system, H-2′), 2.40* (dd, *J*=15.3, 6.6 Hz, A-part of an AB-system, H-2′), 2.48* (dd, *J*=[masked by the solvent] and 6.1 Hz, B-part of an AB-system, H-2′), 2.56 (dd, *J*=16.2, 6.6 Hz, B-part of an AB-system, H-2′), 2.66/2.85* (s, 3H, *N*Me), 3.35* (dd, *J*=11, 8 Hz, H-6), 3.52* (t, *J*=13.1 Hz, H-6), 3.56–3.63 [m, 2H (together with 3.35 and 3.52), H-6], 3.83 (m, 3H, H-3′ and H-6′), 4.73 (m, H-5), 4.95* [m, 3 H (together with 4.73), H-5 and CH_2O], 5.05 (s, 2H, CH_2O), 5.22 (s, 2H, CH_2O), ≈6. 8 (br. s, 1H, NH), 6.98/7.08* (d, 1H, *J*=5.5 Hz, ZNH–C-3′), 7.23–7.40 (m, 15H), 9.11 (br. s, 2H, NH) and ≈9.6 (br. s, 2H, NH); ^{13}C NMR (75.5 MHz, [D_6]DMSO, signals of the major rotamer are marked with ∗) δ 25.2 (CH_2), 29.5/33.0 (*N*Me), 31.3 (CH_2), 44.6 (CH_2), other signals of CH_2-groups are masked by the signals of [D_6]DMSO, 47.8*/47.9 (CH), 52.1*/54.2 (CH), 65.1, 66.2, 68.2 (CH_2O), 127.53, 127.66, 127.71, 127.79, 127.82, 127.88, 128.27, 128.32, 128.5 (CH), 135.3, 137.1, 137.2 (C), 155.0*/155.5, 155.6 (NCO), 159.7, 162.9, 170.9*/171.1 (CO); ESI-MS (positive mode), *m*/*z* (rel. int., %) 780 (100) [M+Na^+], 758 (84) [M+H^+].

4.1.16. (3′*S*,5*S*)-3,4,5,6-Tetrahydro-5-[*N*-methyl-*N*-(β-homoarginyl)amino]-2-ureidopyrimidin-4-one dihydrochloride (TAN-1057A*2HCl). A suspension of the coupling product (*S*,*S*)-**21a** (205 mg, 0.271 mmol) and $PdCl_2$ (48.5 mg, 0.274 mmol) in anhydrous MeOH (7 mL) was flushed with nitrogen and then with hydrogen, and was vigorously stirred under hydrogen (a balloon with H_2 was attached). Gradually, the light-brown suspension turned gray, and then the starting material dissolved. After stirring for about 3–4 h at room temp. (28 °C), the reaction was complete. After flushing with N_2, the reaction mixture was filtered through Celite® to remove the Pd-black. The filter-cake was washed with MeOH (3×3 mL), and the filtrate was evaporated in vacuo. The colorless solid residue was triturated with anhydrous ether (10 mL), collected on a filter under ether, quickly washed with ether once more (10 mL), and dried in vacuo (0.01 mm Hg) overnight to give 122 mg of the title compound (106% yield, 6% w/w of MeOH) as an amorphous white powder. $[\alpha]_D^{22}=-22.7$ (*c* 0.6, water);[16] lit.:[2] $[\alpha]_D^{22}=-39.1$ (*c* 0.53, water); CD spectrum θ (λ, nm, water)=+12,500 (215), −12,600 (233), −7500 (253), −14,200 (269); lit.[2] θ (λ, nm, water)=+13,300 (215), −13,500 (231), −13,500 (267); IR: ν=3340, 3156, 1747, 1653, 1615, 1420, 1378, 1277, 1218, 1135, 1013 cm^{-1}; ^{1}H NMR ([D_4]MeOH, 600 MHz) δ 1.71, 1.80 (2 m, 4H, H-4′ and H-5′), 2.79 (dd, *J*=17.4, 9 Hz, 1H, H-2′), 2.97 (dd, *J*=17.4, 3.8 Hz, 1H, H-2′), 2.88/3.12 (2 s, $\sum$ 3H, *N*Me), 3.25 (t, *J*=6.8 Hz, 2H, H-6′), 3.61 (m, 1H, H-3′), 3.81 (dd, *J*=12.9, 7.9 Hz, 1H, H-6), 3.95 (t, *J*=12.9 Hz, 1H, H-6), 5.19 (dd, *J*=8.7, 12.7 Hz, 1H, H-5); ^{13}C NMR (75.5 MHz [D_4]MeOH,) δ 25.8 (C-5′), 30.8 (C-4′), 35.1 (*N*Me), 36.1 (C-2′), 40.2 (C-6), 42.0 (C-6′), 49.6 (C-3′), 54.9 (C-5), 156.3, 156.7, 156.8 (NCO), 170.5, 173.0 (CO); ESI-MS (positive mode), *m*/*z* (rel. int., %) 356 (100) [M+H^+].

4.1.17. (3′*S*,5*S*)-5-[*N*-Methyl-*N*-[3′,6′-bis(benzyloxycarbonylamino)hexanoyl]amino]-5,6-dihydro-2-ureidopyrimidin-4(1*H*)-one [(*S*,*S*)-21b]. The title compound was obtained from the acid (*S*)-**20b** (317 mg, 0.77 mmol) and (*S*)-**1** (142 mg, 0.77 mmol; e.e.=87%) in anhydrous DMF (4 mL) with HATU (585 mg, 1.54 mmol) and DIEA (199 mg, 1.54 mmol) as described for the coupling product (*S*,*S*)-**21a**. After recrystallization from a mixture of CH_2Cl_2 and EtOAc, 370 mg (83%) of the title compound with de=90% was obtained; $[\alpha]_D^{20}=-93$ (*c* 1.03, DMF). In another experiment, (*S*)-**1** (1.20 g, 6.48 mmol) of lower optical purity ($[\alpha]_D^{20}=-213$ (*c* 0.48, DMF), e.e.≈75%), acid (*S*)-**20b** (2.69 g, 6.49 mmol), HATU (4.90 g, 12.9 mmol) and DIEA (2.22 mL, 1.74 g, 13.5 mmol) in 15 mL of DMAA gave 2.74 g (73%) of the crude (*S*,*S*)-**21b**, which was twice recrystallized from a mixture of CH_2Cl_2 and EtOAc to afford 2.09 g (55%) of the title compound with de=85%; (3′*S*,5*R*)-isomer: R_t=14.38 min, (3′*S*,5*S*)-isomer:

R_t=20.77 min (Chiracel OD-H, column 250×2 mm, heptane/isopropanol, 1:1, 0.2 mL/min); (3′*S*,5*R*)-isomer: R_t=15.99 min, (3′*S*,5*S*)-isomer: R_t=26.52 min (Chiralpak OD-H, column 250×4.6 mm, methanol, 0.5 mL/min). Found C 57.63, H 6.14, N 16.49; calcd for $C_{28}H_{35}N_7O_7$ (581.6) C 57.82, H 6.06, N 16.86; IR: ν=3335, 3148, 2940, 1716, 1698, 1643, 1610, 1576, 1528, 1455, 1404, 1347, 1271, 1141, 1069, 1026 cm^{-1}; ^1H NMR ([D$_6$]DMSO, 600 MHz, signals of the major rotamer are marked with ∗) δ 1.37 and 1.45 (2 m, 4H, H-4′ and H-5′), 2.24 (dd, *J*=14.5, 6.4 Hz, A-part of an AB-system, H-2′), 2.43∗ (dd, *J*=15.6, 6.4 Hz, A-part of an AB-system, H-2′), 2.52∗ (dd, *J*=15, 6 Hz, B-part of an AB-system, H-2′), 2.58 (dd, *J*=15.7, 6 Hz, B-part of an AB-system, H-2′), 2.67/2.90∗ (s/br. s∗, 3H, *N*Me), 2.97 (br. s, 2H, H-6′), 3.40∗ (dd, *J*=12.3, 7.8 Hz, H-6), 3.56∗ (t, *J*=12.9 Hz, H-6), 3.59–3.65 [m, 2H (together with 3.40 and 3.56), H-6], 3.80/3.84∗ (br. s, 1H, H-3′), 4.78 (m, H-5), 5.05 [br. s, 5H (together with 4.78), 2×CH_2O], ≈6.8 (br. s, 1H, NH), 6.99/7.09∗ (d, 1H, *J*=5.5 Hz, ZNH-C-3′), 7.23–7.40 (m, 10H), ≈9.8 (br. s, 2H, NH). ^{13}C NMR (75.5 MHz, [D$_6$]DMSO, signals of the major rotamer are marked with ∗) δ 26.3 (C-5′), 29.5/33.1∗ (*N*Me), 31.6 (C-4′), 47.8∗/48.2 (C-3′), 52.1∗/54.1 (C-5), 65.2 (CH_2O), 127.6, 127.7, 128.3 (CH), 137.3 (C), 155.7, 156.1 158.5 (br.) (NCO), 171.0∗/171.2, 173.1∗/174.0 (CO). ESI-MS (positive mode), *m*/*z* (rel. int., %) 1185 (100) [2M+Na$^+$], 604 (92) [M+Na$^+$]; (positive mode) 580 (100) [M−H$^+$].

4.1.18. (3′*S*,5*S*)-3,4,5,6-Tetrahydro-5-[*N*-methyl-*N*-(3,6-diaminohexanoyl)amino]-2-ureidopyrimidin-4-one dihydrochloride [(*S*,*S*)-22b]. The coupling product (*S*,*S*)-**21b** (268 mg, 0.461 mmol, de=90%) with added $PdCl_2$ (81.7 mmol, 0.461 mmol) in anhydrous MeOH (15 mL) was hydrogenated and worked-up as described above for the preparation of TAN-1057A∗2HCl to give 193 mg (108% yield, 8% w/w of MeOH) of the title compound as an amorphous powder. HRMS *m*/*z* (ESI) found 314.1913, calcd for $C_{12}H_{24}N_7O_3$ [M+H$^+$] 314.1941; found 627.3810, calcd for $C_{24}H_{47}N_{14}O_6$ [2M+H$^+$] 627.3810; $[\alpha]_D^{22}$=+0.6 (*c* 1.0, water); CD spectrum θ (λ, nm, water)=+13,800 (215), −11,700 (235), −6900 (254), −12,000 (266); IR: ν=3343, 3127, 3010 sh, 2893, 1778, 1747, 1683, 1623, 1576, 1490, 1380, 1284, 1212, 1123, 1085, 1012 cm^{-1}; ^1H NMR ([D$_4$]MeOH, 600 MHz) δ 1.81 (br. s, 4H, H-4′ and H-5′), 2.81 (dd, *J*=17.6, 8.5 Hz, 1H, H-2′), 2.98 (dd, *J*=17.1, 4.1 Hz, H-2′), 2.99 (br. s, $\sum$ 3H, H-6′), 2.89/3.16 (2 s, $\sum$ 3H, *N*Me), 3.62 (br. s, 1H, H-3′), 3.89 (dd, *J*=13.5, 7.9 Hz, 1H, H-6), 4.02 (t, *J*=12.9 Hz, 1H, H-6), 5.17 (dd, *J*=7, 12 Hz, H-5); ^{13}C NMR ([D$_4$]MeOH, 75.5 MHz) δ 24.5 (C-5′), 30.6 (C-4′), 35.6 (*N*Me), 36.0 (C-2′), 40.2 (C-6/C-6′), 40.0 (C-6/C-6′), 49.4 (C-3′), 55.4 (C-5), 154.1, 155.3 (NCO), 166.6, 172.8 (CO). ESI-MS (positive mode), *m*/*z* (rel. int., %) 627 (18) [2M+H$^+$], 314 (100) [M+H$^+$]; (negative mode) 348 (50) [M+Cl$^-$], 312 (100) [M−H$^+$].

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References and notes

1. Katayama, N.; Fukusumi, S.; Funabashi, Y.; Iwahi, T.; Ono, H. *J. Antibiot.* **1993**, *46*, 606–613.
2. Funabashi, Y.; Tsubotani, S.; Koyama, K.; Katayama, N.; Harada, S. *Tetrahedron* **1993**, *49*, 13–28.
3. Williams, R. M.; Yuan, C. *J. Am. Chem. Soc.* **1997**, *119*, 11777–11784.
4. For the synthesis of analogues of TAN-1057A,B see: (a) Williams, R. M.; Yuan, C.; Lee, V. J.; Chamberland, S. *J. Antibiot.* **1998**, *51*, 189–201. (b) Brands, M.; Es-Sayed, M.; Häbich, D.; Raddatz, S.; Krüger, J.; Endermann, R.; Gahlmann, R.; Kroll, H.- P.; Geschke, F.- U.; de Meijere, A.; Belov, V. N.; Sokolov, V. V.; Kozhushkov, S. I.; Kordes, M. TAN-1057 Derivatives. WO 00/12484.. (c) Brands, M.; Endermann, R.; Gahlmann, R.; Krüger, J.; Raddatz, S.; Stoltefuβ, J.; Belov, V. N.; Nizamov, S.; Sokolov, V. V.; de Meijere, A. *J. Med. Chem.* **2002**, *45*, 4246–4253. (d) Brands, M.; Endermann, R.; Gahlmann, R.; Krüger, J.; Raddatz, S. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 241–246. (e) Brands, M.; Grande, Y. G.; Endermann, R.; Gahlmann, R.; Krüger, J.; Raddatz, S. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2641–2645.
5. For the synthesis of the racemic heterocycle (*RS*)-**1** and TAN-1057A/B from the racemic precursors (*RS*)-**14**, (*RS*)-**15** and (*RS*)-**4**, see: Sokolov, V. V.; Kozhushkov, S. I.; Nikolskaya, S.; Belov, V. N.; Es-Sayed, M.; de Meijere, A. *Eur. J. Org. Chem.* **1998**, 777–783.
6. The yield of (*RS*)-**1** has been substantially improved (70% vs. initially reported 35%), by using MeCN as a solvent instead of *i*PrOH (8 mL per 1 mmol of (*RS*)-**4** and **5**), decreasing the reaction temperature from 90 to 55 °C, and increasing the reaction time up to 48 h. An amount of base (AcONa) was the same as described previously.[5] After 2 days, the solvent was removed in vacuo, and the solid residue was shaken with 3% aq. $NaHCO_3$ (1 mL per 1 mmol of the starting materials). Further isolation procedure was identical to the already described one.[5]
7. (a) Waki, M.; Kitajima, Y.; Izumiya, N. *Synthesis* **1981**, 266–268. (b) Otsuka, M.; Kittaka, A.; Iimori, T.; Yamashita, H.; Kobayashi, S.; Ohno, M. *Chem. Pharm. Bull.* **1985**, *33*, 509–514.
8. Schwarz, H.; Bumpus, F. M.; Page, I. H. *J. Am. Chem. Soc.* **1957**, *79*, 5697–5703.
9. Valerio, R. M.; Alewood, P. F.; Johns, R. B. *Synthesis* **1988**, 786–789.
10. Olsen, R. K. *J. Org. Chem.* **1970**, *35*, 1912–1915.
11. (a) Aurelio, L.; Box, J. S.; Brownlee, R. T. C.; Hughes, A. B.; Sleebs, M. M. *J. Org. Chem.* **2003**, *68*, 2652–2667. 5-Oxazolidinones from the reaction of hexafluoroacetone and amino acids (simultaneous protection of amino and COOH groups) have already been widely used for the enantioselective synthesis of *N*-methyl amino acids: (b) Burger, K.; Spengler, J. *Eur. J. Org. Chem.* **2000**, 199–204.
12. The overall yield over three of these four steps[11a] was 54% The yield of one step was not specified. The authors[11a] did not report any proof of the optical purity of N^2-*Z*-N^2-Me-L-AsnOH. Identity of the optical rotation value of our sample with >99% e.e. (established by HPLC on a chiral phase

column) with the already reported value[11a] confirms that the authors of the cited publication also managed to prepare the enatiomerically pure compound.

13. Goodmann, H.; Boardmann, F. *J. Am. Chem. Soc.* **1963**, *85*, 2483–2490.
14. Considerable racemization was observed in another attempt to synthesize optically pure (*S*)-**8** from the commercially available *Z*-L-Asp(O*t*Bu)OH (Nova-Biochem). It was methylated with MeI/Ag_2O in DMF to yield *Z*-*N*-Me-L-Asp(O*t*Bu)-OMe. The *tert*-butyl ester was cleaved (Et_3SiH/TFA in CH_2Cl_2), and the ω-COOH group in *Z*-*N*-Me-L-Asp(OH)OMe was converted into the amide (1. EDC, HOBt, THF; 2. aq. NH_3). The N^2-*Z*-N^2-Me-L-AsnOMe thus obtained was oxidatively degraded [$Ph(OCOCF_3)_2$, aq. DMF] to (*S*)-**4**. The overall yield was good, but the enantiomeric excess was found to be only about 40% ($[\alpha]_D^{20}=-42$ (*c* 1.1, MeOH)).
15. An alternative synthesis of the β-amino acid (*S*)-**20a** by Wolff-rearrangement of the diazoketone (*S*)-**19** catalyzed by silver benzoate was described in the Supporting Information of Ref. 3.
16. Our sample of TAN-1057A*2HCl contains ca. 1 mol of MeOH per 1 mol of the hydrochloride salt. This corresponds to ca. 7% (w/w) of MeOH. Corrected $[\alpha]_D^{22}=-24$ (*c* 0.6, H_2O). As reported in Ref. 5 the residual amount of MeOH could not be removed even by prolonged drying in high vacuum.
17. For recent data concerning the pharmacology of (*S*)-N^2-methyl-2,3-diaminopropionic acid derivatives, see: (a) Olson, R. E.; Sielecki, T. M.; Wityak, J.; Pinto, D. J.; Batt, D. G.; Frietze, W. E.; Liu, J.; Tobin, A. E.; Orwat, M. J.; Di Meo, S. V.; Houghton, G. C.; Lalka, G. K.; Mousa, S. A.; Racanelli, A. L.; Hausner, E. A.; Kapil, R. P.; Rabel, H. R.; Thoolen, M. J.; Reilly, T. M.; Anderson, P. S.; Wexler, R. R. *J. Med. Chem.* **1999**, *42*, 1178–1192. (b) Larsen, S. D.; Connell, M. A.; Cudahy, M. M.; Evans, B. R.; May, P. D.; Meglasson, M. D.; O'Sullivan, T. J.; Schostarez, H. J.; Sih, J. C.; Stevens, F. C.; Tanis, S. P.; Tegley, C. M.; Tucker, J. A.; Vaillancour, V. A.; Vidmar, T. J.; Watt, W.; Yu, J. H. *J. Med. Chem.* **2001**, *44*, 1217–1230. (c) Xue, C.-B.; Wityak, J.; Sielecki, T. M.; Pinto, D. J.; Batt, D. G.; Cain, C. A.; Sworin, M.; Rockwell, A. L.; Roderick, J. J.; Wang, S.; Orwat, M. J.; Frietze, W. E.; Bostrom, L. L.; Liu, J.; Higley, C. A.; Rankin, F. W.; Tobin, A. E.; Emmett, G.; Lalka, G. K.; Sze, J. Y.; Di Meo, S. V.; De Grado, W. F.; Wexler, R. R.; Olson, R. E. *J. Med. Chem.* **1997**, *40*, 2064–2084.
18. (a) Parkanyi, C.; Yuan, H. L.; Cho, N. S.; Jaw, J.-H.; Woodhaus, T. E.; Aung, T. L. *J. Heterocycl. Chem.* **1989**, *26*, 1331–1334. (b) Klaymann, D. L.; Shine, R. J.; Bower, J. D. *J. Org. Chem.* **1972**, *37*, 1532–1537.
19. This compound (with an unknown degree of racemization and an unknown optical rotation value) was also found to be an oil: see Supporting Information of Ref. 3.
20. Data for the monohydrate of the title compound from the Supporting information to Ref. 3. Relative amounts of the solvents are not given.