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Asymmetric total synthesis of natural diheteropeptin

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Abstract—A total asymmetric synthesis of diheteropeptin and a stereomer from the known (*E*)-1-iodo-6-octene, using the Schöllkopf method for amino acid synthesis and Sharpless asymmetric dihydroxylation as key steps, is described. The asymmetric synthesis of a new unsaturated amino acid is also described. © 2001 Elsevier Science Ltd. All rights reserved.

Transforming growth factors β (TGF-β) are multifunctional cytokines, first discovered as trophic factors for several different cell lines.[1] They act as regulators of immune function, cell proliferation and differentiation, as well as extra-cellular matrix production. Substances that mimic TGF-βs action are thus expected to be useful for treatment of diseases such as ischemia injury, cancer or for improving healing process.[2–6] A screening aimed at the discovery of TGF-β agonists led recently Y. Masuoka and co-workers to isolate from the fermentation broth of *Diheterospora chlamydospora* Q 58044 a cyclic tetrapeptide named diheteropeptin **1** (Fig. 1), which demonstrates TGF-β like biological properties.[7,8] In this first report, the authors did not assign the stereochemistry of the five chiral centers but mentioned the high structural similarity with chlamydocin **2**, an antitumoral agent isolated from the same microorganism and whose structure was fully characterized as *cyclo*-(2-aminoisobutyryl-(*S*)-L-phenylalanyl-(*R*)-prolyl-(2*S*,9*S*)-2-amino-8-oxo-9,10-epoxidecanoyl)

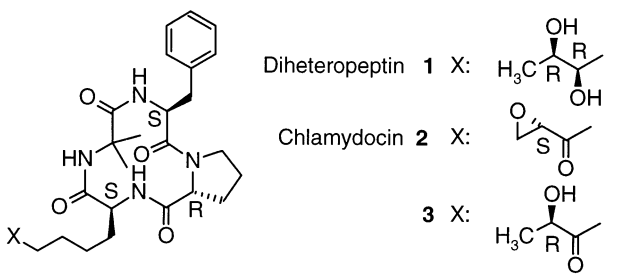

Figure 1.

(Fig. 1).[9] It is worth noting that another closely related compound **3**, isolated from *Verticillium coccosporum*, presents the same peptidic backbone stereochemistry.[10]

We were interested in obtaining diheteropeptin **1** and decided to develop an asymmetric synthesis that can also give access to various analogs. In order to avoid the synthesis of the 32 possible stereomers, we first made the assumption that the stereochemistry of the peptidic backbone of diheteropeptin is the same as that of **2** and **3**. We thus planned the synthesis of the four residual stereomers resulting from the presence of the two chiral centers, C-8 and C-9, of the diol part of the molecule. Very recently, Y. Masuoka and co-workers have fully characterized the absolute configuration of the five chiral centers, as shown in Fig. 1, using NMR, CD data and chemical degradation into derivatives of known absolute configuration.[11] This work confirmed our assumption and prompted us to publish our work on the total synthesis of diheteropeptin. A lot of work has been described on the synthesis of the related molecules chlamydocin and analogs that helped us to conceive our retro-synthetic scheme.[12–19] The synthesis of diheteropeptin is described herein via a route in which the dihydroxy amino acid is formed by asymmetric dihydroxylation (AD) of (2*S*,8*E*)-2-aminodec-8-enoic acid after it has been incorporated in the tetrapeptide ring precursor **11**. The exotic amino acid (2*S*,8*E*)-2-aminodec-8-enoic acid **8** has never been described. Its asymmetric synthesis has been realized from 1,5-pentanediol, as described in Scheme 1. The protected methyl alkyne **5** was obtained from commercially available 1,5-pentanediol in four steps, as described by R. Gruiec and co-workers.[20] The stereoselective *trans* reduction of the alkyne with $LiAlH_4$ firstly required deprotection of the alcoholic function.[21] The transformation of the (*E*)-olefinic alcohol into its corre-

Keywords: asymmetric dihydroxylation; amino acid synthesis; diheteropeptin; cyclic peptide.

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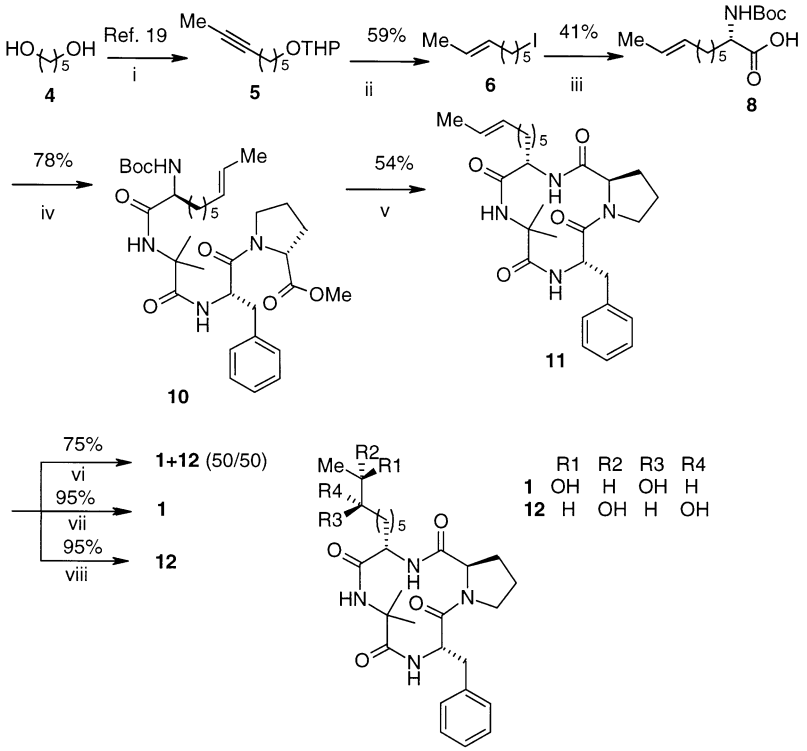

Scheme 1. (i) (a) $Ph_3P{\cdot}Br_2$, DMF, (b) DPH, APTS, CH_2Cl_2, (c) HCCLi·EDA, DMSO, (d) CH_3I, BuLi, THF/HMPA; (ii) (a) MeOH, APTS, (b) $LiAlH_4$, diglyme/THF, (c) CH_3SO_2Cl, TEA, CH_2Cl_2, (d) LiI, Et_2O; (iii) (a) *n*-BuLi, THF, **7**, −78°C to rt, (b) HCl 0.25 M, rt, (c) Boc_2O, DIEA, rt, CH_2Cl_2, (d) LiOH, DME, H_2O, rt; (iv) Aib-(L)-Phe-(D)-Pro-OMe **9**, PyBOP®, DIEA, CH_2Cl_2, rt; (v) (a) LiOH, DME, H_2O, rt, (b) TFA, CH_2Cl_2, (c) PyBOP®, DIEA, CH_2Cl_2 (10^{-3} M); (vi) OsO_4, NMO; (vii) AD-mix-β, $CH_3SO_2NH_2$, H_2O, *t*-BuOH, 0°C, 2 h; (viii) AD-mix-α, $CH_3SO_2NH_2$, H_2O, *t*-BuOH, 0°C, 2 h.

sponding iodo derivative was first tested using Ph_3P/I_2/imidazole iodination reagent[22] but we were confronted with scale-up problems and the two-step conversion using LiI on the methanesulfonate intermediate was found to be more efficient.[23] The stereoselective (d.e. 80%) synthesis of the exotic *S* amino acid was realized with the Schöllkopf method[24] using the commercially available bis-lactim ether of cyclo(D-Val-Gly) **7**. The chromatographic elimination of valine methyl ester by-product must be performed before Boc amino-protection because its separation from the desired product is very difficult. The enantiomeric purity (e.e. 96%) of the methyl ester of (2*S*,8*E*)-2-aminodec-8-enoic acid has been determined by HPLC after derivatization with Mosher's acid[25] and was supposed to be *S*, according to the empiric rule of the electrophile addition which should be *anti* to the methyl group of the bis-lactim ether.[24a] Saponification of the methyl ester derivative with lithium hydroxide, followed by coupling of the resulting acid **8**[26] with tripeptide **9** using PyBOP® reagent,[27] led to the protected tetrapeptide **10**.[28] We chose this peptide from the four possible peptidic sequences in order to facilitate the ring closure according to the results obtained in an extensive study conducted for chlamydocin synthesis optimization.[12] The cyclization was performed in good yield, under high dilution conditions, using PyBOP® as the coupling agent after deprotection of the terminal amino and carboxylic functions. At this stage, the dihydroxylation could be made non-stereoselectively using OsO_4/NMO reagent to afford an inseparable equimolecular mixture of the two stereomers **1** and **12**, as determined by ^{13}C NMR spectroscopy. Pure diheteropeptin **1**[29] has been obtained using Sharpless asymmetric dihydroxylation of **11**[30] using commercially available dihydroquinidine-derived reagent AD-mix-β, according to the predictive mnemonic rules for the synthesis of the (*R*,*R*) stereomer.[31] The reaction is stereospecific due to the fact that we could not detect any trace of the other stereomer by ^{13}C NMR. The obtained product has exactly the same NMR spectroscopic characteristics as those described by Y. Masuoka and co-workers. The stereomer **12**[32] was obtained similarly using the commercial AD-mix-α with the same diastereomeric purity showing no influence on the chirality of the peptidic backbone on the stereochemical course of the reaction. The ^{13}C NMR chemical shifts of the carbons bearing the hydroxyl groups of this stereomer **12** (70.82 and 76.00 ppm) are slightly different from those of natural diheteropeptin **1** (70.90 and 76.13 ppm). This has been used to check the diastereomeric purity of the product since we were unable to determine it using a chromatographic method. In conclusion, we have achieved the first total asymmetric synthesis of the natural product diheteropeptin starting from the known 2-oct-6-ynyloxytetrahydropyran **5** in 12 steps with an overall yield of 9.7%. Furthermore, this approach confirms the empirical rules established for Schöllkopf and Sharpless asymmetric reactions and will allow the synthesis of other stereomers and analogs of diheteropeptin suscep-

tible to demonstrate TGF-β activity. These results will be published in the near future.

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26. **(2*S*,8*E*)-2-[(*tert*-Butoxycarbonyl)amino]dec-8-enoic acid (8)**: R_f 0.2 [cyclohexane–EtOAc (40:60)]; $[\alpha]_D^{26}=-2.0°$ (*c* 0.19, MeOH); δ_H (300 MHz, d_6-DMSO): 1.10–1.45 (15H, m), 1.50–1.70 (5H, m), 1.85–2.00 (2H, m), 3.75–3.90 (1H, m), 5.30–5.50 (2H, m), 7.01 (1H, d, $J=8.0$ Hz), 12.0–13.0 (1H, bs); δ_C (75.47 MHz, d_6-DMSO): 17.71, 25.37, 28.07, 28.19, 28.84, 30.75, 31.88, 53.36, 77.86, 124.38, 131.25, 155.58, 174.28. IR 1712, 1503, 1397, 1366 cm^{-1}. ESI^+-MS (MH^+): 286. Anal. calcd for $C_{15}H_{27}NO_4$: C, 63.13; H, 9.54; N, 4.91. Found: C, 62.84; H, 9.74; N, 5.22.
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28. **Methyl *N*-[2-({(2*S*,8*E*)-2-[(*tert*-butoxycarbonyl)amino]dec-8-enoyl}amino)-2-methylpropanoyl]-L-phenylalanyl-D-prolinate (10)**: mp 42°C; R_f 0.3 [cyclohexane–EtOAc (40:60)]; $[\alpha]_D^{22}=+35.5°$ (*c* 0.18, MeOH); δ_H (300 MHz, $CDCl_3$): 1.20–1.70 (26H, m), 1.75–2.10 (6H, m), 2.70–3.20 (3H, m), 3.50–3.65 (1H, m), 3.69 (3H, s), 3.85–4.05 (1H, m), 4.25–4.35 (1H, m), 4.85–4.95 (1H, m), 5.00–5.10 (1H, bs), 5.35–5.45 (2H, m), 6.73 (1H, s), 6.85 (1H, d, $J=8.2$ Hz), 7.15–7.35 (5H, m); δ_C (75.47 MHz, $CDCl_3$): 17.87, 24.40, 24.58, 25.28, 25.42, 28.30 (3), 28.78, 28.94, 29.34, 32.17, 32.39, 39.22, 46.72, 52.15, 52.57, 55.07, 56.98, 58.77, 80.10, 124.76, 126.92, 128.36 (2), 129.54 (2), 131.33, 136.37, 155.79, 169.61, 171.56, 172.16, 173.56; IR 1740, 1670, 1635, 1503, 1451 cm^{-1}; ESI^+-MS (MH^+): 629. Anal. calcd for $C_{34}H_{52}N_4O_7$: C, 64.94; H, 8.34; N, 8.91. Found: C, 64.31; H, 8.48; N, 8.78.
29. **(3*S*,9*S*,14a*R*)-9-Benzyl-3-[(6*R*,7*R*)-6,7-dihydroxyoctyl]-6,6-dimethyldecahydropyrrolo[1,2-*a*][1,4,7,10]tetraazacyclododecine-1,4,7,10-tetrone (1)**: mp 82°C (lit.[7] 74–76°C); R_f 0.12 [EtOAc]; $[\alpha]_D^{25}=-55.6°$ (*c* 0.19, MeOH) [lit.[7] $[\alpha]_D^{25}=-30.3°$ (*c* 0.19, MeOH)]; δ_H (300 MHz, $CDCl_3$): 1.20 (3H, d, $J=6.3$ Hz), 1.25–1.95 (19H, m), 2.10–2.45 (4H, 2 exchangeable, m), 2.94 (1H, dd, $J=5.5$ Hz, 13.5 Hz), 3.15–3.40 (3H, m), 3.55–3.65 (1H, m), 3.80–3.90 (1H, m), 4.15–4.25 (1H, m), 4.65 (1H, dd, $J=2.0$, 8.0 Hz), 5.15 (2H, dt, $J=5.5$, 10.0 Hz), 6.09 (1H, s), 7.14 (1H, d, $J=10$ Hz), 7.20–7.35 (5H, m), 7.52 (1H, d, $J=10$ Hz); δ_C (75.4 MHz, $CDCl_3$): 19.50, 23.57, 24.70, 24.99, 25.28 (2), 26.44, 28.85, 29.13, 33.01, 35.82, 46.95, 53.40, 54.39, 57.76, 58.76, 70.90, 76.13, 126.68, 128.57 (2), 129.00 (2), 136.97, 171.89, 172.83, 174.43, 175.56; IR (KBr): 3400, 3300, 1680, 1670, 1660, 1620, 1520 cm^{-1}; ESI^--MS $(M-H)^-$ 529. Anal. calcd for $C_{28}H_{42}N_4O_6\cdot 0.67H_2O$: C, 61.96; H, 8.05; N, 10.32. Found: C, 61.51; H, 7.86; N, 10.37.
30. **(3*S*,9*S*,14a*R*)-9-Benzyl-6,6-dimethyl-3-[(6*E*)-oct-6-enyl]-decahydropyrrolo[1,2-*a*][1,4,7,10]tetraazacyclododecine-1,4,7,10-tetrone (11)**: R_f 0.5 [cyclohexane–EtOAc (50:50)]; mp 55°C; $[\alpha]_D^{26}=-60.4°$ (*c* 0.19, MeOH); δ_H (250 MHz, $CDCl_3$): 1.1–1.4 (6H, m), 1.34 (3H, s), 1.77 (3H, s), 1.55–2.05 (12H, m), 2.10–2.40 (2H, m), 2.95 (1H, dd, $J=5.8$, 13.5 Hz), 3.15–3.35 (2H, m), 3.8–3.9 (1H, m), 4.18 (1H, dt, $J=7.5$, 10.3 Hz), 4.65 (1H, dd, $J=2.5$, 8.0 Hz), 5.10–5.25 (1H, m), 5.35–5.45 (2H, m), 5.90 (1H, s), 7.07 (1H, d, $J=10.2$ Hz), 7.15–7.35 (5H, m), 7.53 (1H, d, $J=10.2$ Hz); δ_C (62.9 MHz, $CDCl_3$): 17.90, 23.54, 24.72, 25.01, 25.38, 26.51, 28.72, 28.89, 29.25, 32.36, 35.77, 46.96, 53.41, 54.39, 57.76, 58.77, 124.79, 126.67, 128.58 (2), 129.02 (2), 131.28, 137.04, 171.74, 172.74, 174.42, 175.65; IR 1662, 1626, 1523 cm^{-1}; ESI^--MS $(M-H)^-$: 495. Anal. calcd for $C_{28}H_{40}N_4O_4\cdot 0.55H_2O$: C, 66.39; H, 8.18; N, 11.06. Found: C, 63.97; H, 8.29; N, 11.26.
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32. **(3*S*,9*S*,14a*R*)-9-Benzyl-3-[(6*S*,7*S*)-6,7-dihydroxyoctyl]-6,6-dimethyldecahydropyrrolo[1,2 - *a*][1,4,7,10]tetraazacyclododecine-1,4,7,10-tetrone (12)**: mp 77°C; R_f 0.12 [EtOAc]; $[\alpha]_D^{24} = -67°$ (*c* 0.19, MeOH); δ_H (300 MHz, $CDCl_3$): 1.19 (3H, d, $J = 6.3$ Hz), 1.25–1.95 (19H, m), 2.10–2.45 (2H, m), 2.37 (1H, exchangeable, d, $J = 4$ Hz), 2.47 (H, exchangeable, d, $J = 4.5$ Hz), 2.94 (1H, dd, $J = 5.5$, 13.5 Hz), 3.15–3.40 (3H, m), 3.55–3.65 (1H, m), 3.80–3.90 (1H, m), 4.15–4.25 (1H, m), 4.66 (1H, d, $J = 2.0$, 8.0 Hz), 5.15 (2H, dt, $J = 5.5$, 10.0 Hz), 6.10 (1H, s), 7.14 (1H, d, $J = 10$ Hz), 7.20–7.35 (5H, m), 7.53 (1H, d, $J = 10$ Hz); δ_C (75.4 MHz, $CDCl_3$): 19.50, 23.57, 24.70, 24.99, 25.28 (2), 26.44, 28.85, 29.13, 33.01, 35.82, 46.95, 53.40, 54.39, 57.76, 58.76, 70.82, 76.00, 126.68, 128.57 (2), 129.00 (2), 136.97, 171.89, 172.83, 174.43, 175.56; IR (KBr): 3400, 3300, 1680, 1670, 1660, 1620, 1520 cm^{-1}; ESI^--MS $(M-H)^-$: 529. Anal. calcd for $C_{28}H_{42}N_4O_6 \cdot 0.70H_2O$: C, 61.90; H, 8.05; N, 10.31. Found: C, 61.77; H, 7.98; N, 10.33.