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[15] Crystal structure determination of (*S*,*S*)-**5d**: $[C_{47}H_{23}F_{20}O_3P_2Ru][SbF_6]$; $M_r = 1414.4$; $\mu = 1.018\ mm^{-1}$, $F(000) = 1376$, $\rho_{calcd} = 1.844\ g\,cm^{-3}$, triclinic, $P1$, $Z = 2$, $a = 13.021(1)$, $b = 13.189(1)$, $c = 15.167(2)$ Å, $\alpha = 89.68(1)$, $\beta = 89.22(1)$, $\gamma = 78.05(1)^\circ$, $V = 2548.0(4)$ Å^3, yellow plate $0.18 \times 0.38 \times 0.64$ mm mounted on a quartz fiber with RS3000 perfluoropolyether oil. Intensities were measured at 150 K on a STOE IPDS diffractometer with graphite-monochromated $Mo_{K\alpha}$ radiation ($\lambda = 0.71069$ Å). $2\theta_{max} = 56^\circ$. A total of 43036 measured reflections, 21885 unique reflections (R(int.) = 0.033) of which 21123 were observable ($|F_o| > 4\sigma(F_o)$). Data were corrected for Lorentz and polarization effects and for absorption (T_{min}, T_{max} = 0.6212, 0.8437). The structure was solved by direct methods using MULTAN 87,[26] all other calculations used XTAL[27] system and WebLab ViewerPro[28] program. The absolute configuration was determined and the Flack parameter[29] converged to $x = -0.01(2)$. Full-matrix least-squares refinement based on F using weight of $1/[\sigma^2(F_o) + 0.0003(F_o^2)]$ gave final values $R = 0.045$, $\omega R = 0.055$, and $S = 2.61(2)$ for 1436 variables and 21123 contributing reflections. Hydrogen atoms were placed in calculated positions and other non-disordered atoms were refined with anisotropic displacement parameters. The final difference electron density map showed a maximum of +1.60 and a minimum of −1.47 e Å^{-3}. One of the two molecules shows an *in-plane* disorder of a phenyl group (angle between the two phenyl mean planes = 3.0(6)°). This disorder was resolved by refinement of two tilted positions (tilt angle of about 12°) with population parameters of 0.60 and 0.40, respectively, and restraints on bond lengths, bond angles, and torsional angles (40 restraints). Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-112276. Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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Synthesis and Biological Evaluation of a Cyclo-β-tetrapeptide as a Somatostatin Analogue

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In contrast to small α-peptides, short-chain β-peptides (oligomers of β-amino acids) show a remarkable ability to fold into well defined secondary structures in solution as well as in the solid state.[1] The main three structural elements of proteins (helices, pleated sheets, and turns) have been identified in β-hexapeptides in solution.[2] Cyclic β-peptides arrange in the solid state as tubular structures with a tight net of pleated-sheet-type hydrogen bonds ("nanotubes").[3] The second fundamental difference between natural peptides and β-peptides is the latter's excellent stability against degradation by proteases and peptidases, including the most aggressive ones, such as pronase and proteinase K.[4]

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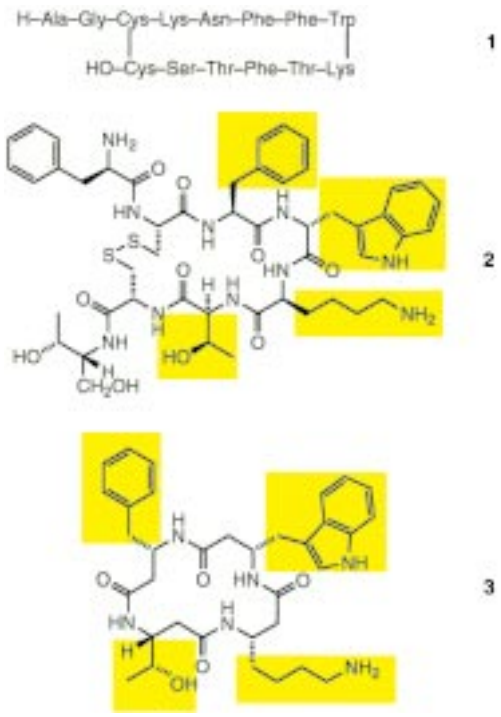
The enzymatic stability and the variety of secondary structures discovered push the door wide open for the application of β-peptides as peptidomimetics in medicinal chemistry. β-Amino acids (in two synthetic steps from the corresponding α-amino acids),[5] as well as β-peptides are readily prepared (by solution or solid-phase methods),[6] allowing their synthesis by combinatorial methods. β-Amino acids have been introduced in pharmacologically active compounds for a long time,[7] and recently the synthesis of conjugates of α- and β-peptides as MHC-class-I protein-binding peptides was reported.[8] However, to the best of our knowledge, there is no report in the literature about the pharmacologic potential of β-peptides as biologically active compounds. Thus, the question whether β-peptides can mimic natural α-peptides in their recognition by (human) receptors is hitherto unanswered.

We chose the natural α-peptide hormone somatostatin ($SRIF_{14}$, **1**), isolated in 1973 by Guillemin et al. from 500 000 hypothalami. This peptide has various important biological functions, for example the regulation of the release of growth hormone and insuline.[9] Octreotide (SANDOSTATIN, **2**), a cyclic α-octapeptide derived from the tetradecapeptide somatostatin, is clinically in use to treat acromegaly and certain



intestine cancers.[10] However, the elimination half-life of **2** (90 min) is still rather short; it is therefore of great importance to find nonpeptidic derivatives with higher bioavailibility. The biologically active conformation of octreotide, a β-turn, was revealed by structure–activity relationships; the amino acids in the turn (Phe-Trp-Lys-Thr) are required for activity.[10] For the design of a β-peptidic analogue by molecular modeling, we substituted the side chains in the powder X-ray structure of a cyclic all-(*S*)-β-tetrapeptide[3a] with those of Phe, Trp, Lys, and Thr. Superposition of the resulting model (Figure 1, green) with the solution structure of octreotide[11] (Figure 1, gray) gave a good spacial overlap of the side chains, a requirement for biological activity. Therefore, the cyclic β-tetrapeptide **3** was chosen as target for our synthesis.

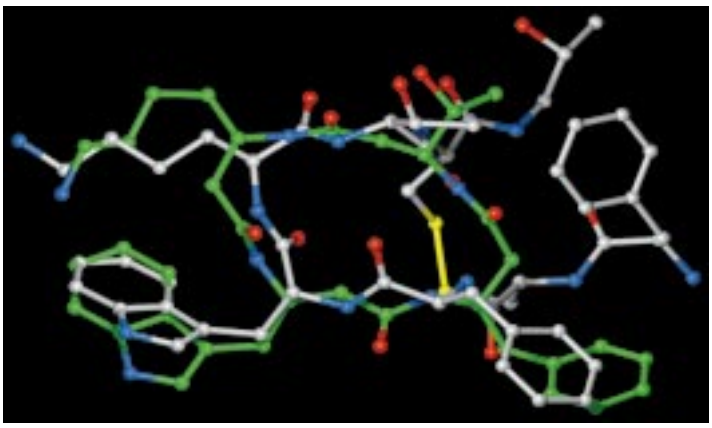
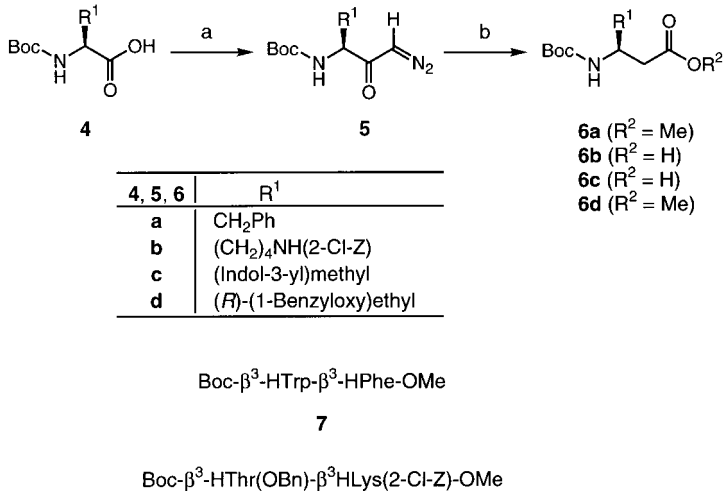


Figure 1. Top view of the superposition of the solution structure of octreotide (**2**) (C atoms in gray)[13] and a model of the somatostatin-analogue **3** derived from the powder X-ray structure of cyclo-(*S*)-(*β*-HAla)$_4$[3a] (C atoms in green). The side chains of **2** and **3** overlap well, a requirement for high affinity.

The β-amino acid building blocks **6a–d** were prepared from the correspondig *N*-Boc-α-amino acids **4a–d** using the Arndt–Eistert reaction via the diazoketones **5a–d** and Wolff rearrangement (Scheme 1). We chose the standard Boc/benzyl-protecting group strategy for peptide synthesis in solution. Boc-deprotection of β-amino ester **6a** and coupling with **6c** gave dipeptide **7**, esterification and Boc-deprotection of **6b**, and coupling with **6d** gave dipeptide **8**; **7** was C- (NaOH solution) and **8** was N-terminally deprotected (CF_3CO_2H), and the resulting fragments were coupled to give the β-tetrapeptide **9** in 93% yield. Compound **9** was deprotected at



4, 5, 6	R^1
a	CH_2Ph
b	$(CH_2)_4NH$(2-Cl-Z)
c	(Indol-3-yl)methyl
d	(*R*)-(1-Benzyloxy)ethyl

Boc-β^3-HTrp-β^3-HPhe-OMe

7

Boc-β^3-HThr(OBn)-β^3HLys(2-Cl-Z)-OMe

8

Scheme 1. Synthesis of β^3-HPhe, β^3-HLys, β^3-HTrp, and β^3-HThr derivatives **6a–d** and of dipeptides **7** and **8**. a) $ClCO_2Et$, Et_3N, THF, then CH_2N_2, Et_2O; **5a**: 53%, **5b**: 50%, **5c**: 59%, **5d**: 69%; b) CF_3CO_2Ag (cat.), Et_3N, THF, R^2OH; **6a**: 94%, **6b**: 89%, **6c**: 89%, **6d**: 88%. Bn = benzyl; Boc = *tert*-butoxycarbonyl; Z = benzyloxycarbonyl.

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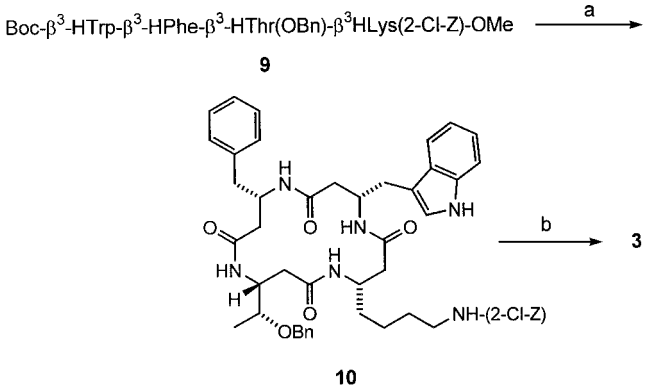
the C-terminus and allowed to react with pentafluorophenol to give the active ester, which, after Boc-deprotection, was cyclized (Hünig base, CH_3CN) to give the cyclo-β-tetrapeptide **10** in good yield (Scheme 2). This peptide is essentially



Scheme 2. The β-tetrapeptide precursor **9** and its cyclization to give **10** and subsequent deprotection to give **3**. a) 1) 50 equiv NaOH, H_2O, DMF, 45 °C, 92 %; 2) C_6F_5OH, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride, DMF/CH_3Cl, quant; 3) CF_3CO_2H, CH_2Cl_2, $(CH_2SH)_2$, quant; 4) *i*$PrNEt_2$, CH_3CN, 70 °C, syringe pump, 48 %; b) Pd/C, H_2, LiCl, THF, MeOH, 48 h, 9 %.[14]

insoluble in all standard solvents used in peptide chemistry.[12] Therefore, we were forced to apply a new method for the hydrogenolysis of the benzyl- and 2-Cl-Z-protecting groups: Peptides can by solubilized in organic solvents such as THF, by the addition of LiCl,[13] but, to the best of our knowledge, hydrogenolysis has never been carried out under these conditions; the cyclo-β-tetrapeptide **10** was solubilized in THF by the addition of six equivalents of LiCl, and could, indeed, be deprotected albeit in poor yields.[14] Purification by reversed-phase HPL chromatography produced **3**.

The affinity of the cyclo-β-tetrapeptide **3** for five different human somatostatin receptors (hsst 1 – 5, expressed in CHO-39 or CCL-39 cell lines) was measured by using radioligand-binding assays (Table 1). Displacement experiments for the specific binding of [^{125}I]LTT-$SRIF_{28}$ to these receptors were carried out as described previously,[15] and the affinities are reported as $pK_d \pm$ SEM values. The data in Table 1 clearly show that **3** has affinity, although the concentrations are in the micromolar and not in the nanomolar range as for **1** and **2** (the affinity is reduced by a factor of 10 (hsst 4) to 10^5 (hsst 2)). Using a glucose-derived somatostatin mimic, a comparable affinity in the micromolar range had been observed.[16]

We have demonstrated for the first time, that a small β-peptide (consisting of only four β-amino acids) can mimic a natural peptide hormone and display biological activity and micromolar affinity for human receptors. Thus, β-peptides can, in principle, be considered as peptidomimetics, also due to their excellent stability against peptidases that might allow for oral bioavailibilty (corresponding experiments with **3** are underway). It appears feasible to use short-chain β-peptides with their compact and well-defined secondary structures as metabolically stable vaccines that could be recognized by human receptors and the immune system.

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Table 1. Comparison of the affinities of cyclo-β-tetrapeptide **3** and octreotide **2** by radioligand-binding assays (displacement experiments of the specific binding of [^{125}I]LTT-$SRIF_{28}$) with the five different human somatostatin receptors (hsst 1 – 5, expressed in two different cell lines). The values are reported as $pK_d \pm$ SEM (SEM = standard error). The affinities of **3** are in the micromolar range, at least one order of magnitude lower than those of octreotide **2**.[a]

Receptor	β-Peptide **3**	Octreotide (**2**)
hsst-1 CCL39	4.85 ± 0.04	6.65
hsst-2 CCL39	4.44 ± 0.09	9.19
hsst-3 CHO	5.48 ± 0.01	7.88
hsst-4 CCL39	5.00 ± 0.05	6.40
hsst-5 CCL39	3.73 ± 0.15	7.17

[a] CCL-39 = Chinese hamster lung fibroblasts; CHO = Chinese hamster ovaries; hsst = human somatostatin receptor subtype; SRIF = somatotropin release inhibiting factor.

Keywords: hormones · peptides · peptidomimetics · somatostatin

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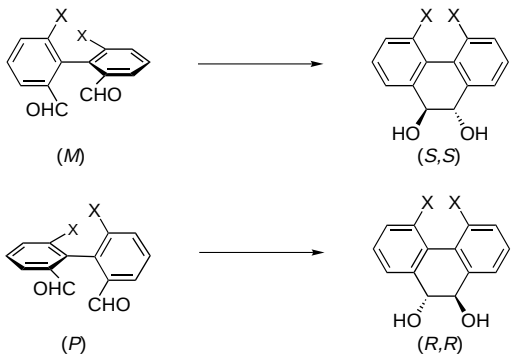
From Axial Chirality to Central Chiralities: Pinacol Cyclization of 2,2′-Biaryldicarbaldehyde to *trans*-9,10-Dihydrophenanthrene-9,10-diol**

Ken Ohmori, Mitsuru Kitamura, and Keisuke Suzuki*

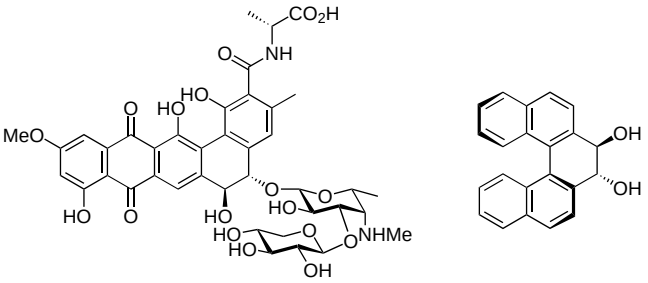
In memory of Vladimir Prelog

We describe herein two salient features of the pinacol cyclization of 2,2′-biaryldicarbaldehydes (Scheme 1): 1) the stereoselectivity to give only the *trans*-diol, and 2) the stereospecificity to transmit the axial chirality (in case the starting



Scheme 1. Chiral transmission.

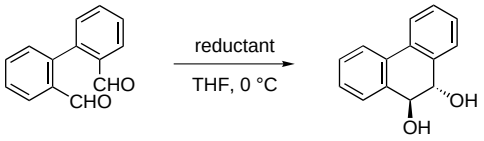
biphenyl is configurationally stable) onto two stereogenic centers of the product. The accessibility of the *trans*-9,10-dihydrophenanthrene-9,10-diol structure has consequences not only to the synthesis of natural products (e.g. **1**),[1] but also to the creation of a new compound such as **2** with potential utility in asymmetric synthesis.[2]



1: pradimicin A **2**

Our initial attempt was centered on the reaction of 2,2′-biphenyldicarbaldehyde (**3**),[3] which upon treatment with SmI_2[4] (2 equiv, THF, 0 °C, 5 min) was cleanly converted into the *trans*-diol **4**[5] as the sole product in 99% yield (Table 1, run 1). To our knowledge, the *intramolecular* pinacol coupling of two aromatic aldehydes is unprecedented,[6] as opposed to many *intermolecular* examples.[7] The observed *trans* selectivity stands in contrast to the *cis* selectivity generally seen for aliphatic 1,6-dicarbonyl compounds.[7, 8]

Table 1. Pinacol cyclization of **3** with various reductants.



3 **4**

Run	Reductant	Yield [%]	*trans*/*cis* of **4**
1	SmI_2	99	> 99/1
2	SmI_2, HMPA	93	> 99/1
3	$[VCl_3(THF)_3]$, Zn[a]	93	> 99/1
4	$TiCl_4$, *n*BuLi[b]	80	> 99/1
5	$TiCl_4$, Zn[c]	96	20/1
6	$TiCl_4$, Mg(Hg)[c]	94	16/1
7	Ce, I_2	81	16/1

[a] In CH_2Cl_2. [b] In Et_2O. [c] At −10 °C.

It turned out that consistently high selectivities and yields were attained with various reducing agents (Table 1). Especially, SmI_2 or $[VCl_3(THF)_3]/Zn$[9a] led to perfect *trans* selectivity (runs 1 and 3). Use of a dipolar aprotic cosolvent (hexamethyl phosphoramide, HMPA) did not affect the reaction course (run 2). Use of low-valent titanium or cerium[9b–e] gave a slight decrease in either the selectivity or the yield (runs 4 – 7).

At this stage, we made an analysis on the origin of the selectivity. Taking the *M* isomer as an example (Scheme 2), emergence of the *trans* selectivity could be traced back to two possible modes of reaction with respect to the mutual relation of two aldehyde faces, both with a *like* topicity, *Re*,*Re* and/or *Si*,*Si*. Given that the reaction proceeded uniquely by one of

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