Table III. Double Asymmetric Induction with **7** and **1**.

entry	ene	catalyst	% yield[a]	*syn* : *anti*
1	(*S*)-**7a**	(*R*)-**1**	96 (70)	>99 : <1
2	(*R*)-**7c**	(*S*)-**1**	71 (50)	>99 : <1
3	(*R*)-**7c**	(*R*)-**1**	33 (19)	50 : 50

[a] Calculated value based on the recovery of **7**. Value in parenthesis refers to the isolated yield.

(Table III, entry 2). In contrast, the reaction of (*R*)-**7c** using (*R*)-**1** ("mismatched" catalytic system) affords the diastereomeric mixture (syn/anti = 1/1) in low yield (33%) (entry 3). Furthermore, these results clearly show that the alkoxy group acts as a controlling element not only for stereo- but also for regiocontrol.[18]

In summary, we have demonstrated that the chiral titanium complex catalyzed glyoxylate–ene reactions involving prochiral and chiral ene components provide remarkably high levels of remote asymmetric induction through asymmetric desymmetrization and chiral recognition during the C–C bond formations.

Acknowledgment. The authors are grateful to Professor Takeshi Nakai for his continuous encouragement and useful discussions. The authors are also grateful to Professor Thomas R. Hoye for his comments and useful discussions. This research was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Japan, the Asahi-Kasei Award in Synthetic Organic Chemistry, Japan, and the Iwaki Scholarship Foundation.

Supplementary Material Available: Typical experimental procedures for the kinetic resolution and physical data of the ene products (**4** and **5**) and recovered **7** (3 pages). Ordering information is given on any current masthead page.

(17) This number is obtained from the following equation: $\ln [(1-c)(1-ee_{recov})]/\ln [(1-c)(1+ee_{recov})]$, $c = ee_{recov}/(ee_{recov}+ee_{prod})$, $0 < c$, $ee < 1$ where c is the fraction of consumption of racemate. Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237. See also: Wang, Y.-F.; Chen, C.-S.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1984**, *106*, 3695.

(18) It is rather surprising that only one regioisomer was obtained, in sharp contrast to the low-to-moderate level of regioselectivity in the competitive case of methyl vs methylene or methine hydrogen shift.[5c] For the controlling effect of alkoxy groups of (homo)allylic ethers in the regio- and stereochemistries of carbonyl–ene reactions, see: Mikami, K.; Shimizu, M.; Nakai, T. *J. Org. Chem.* **1991**, *56*, 2952.

Vinylogous Polypeptides: An Alternative Peptide Backbone

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Despite the bewildering array of tertiary structures exhibited by polypeptide chains (i.e., proteins), it is remarkable that only two types of ordered secondary structures are observed: helices and sheets. An important early advance in protein chemistry was the successful prediction of these structural elements.[1] We have attempted to analyze the secondary and tertiary structure of polypeptide chains of building blocks not based on amino acids, but on derivatives of amino acids. The preparation of such materials is hoped to yield new classes of protein-like substances with alternative backbones. The initial system we chose to study consists of repeating units of extended amino acids that have an (*E*)-ethenyl unit inserted between the carbonyl carbon and Cα (vinylogous amino acids, **1**[2]). We now report the synthesis[3] and conformational analysis of vinylogous polypeptides **2** and the observation of their novel secondary structures by a combination

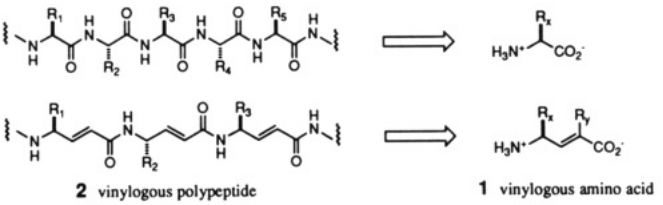
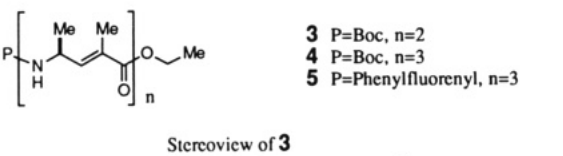


Figure 1. Comparison of polypeptides and vinylogous polypeptides.



Stereoview of **3**

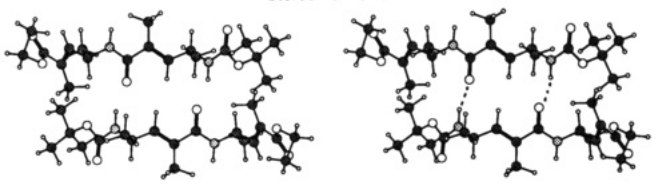
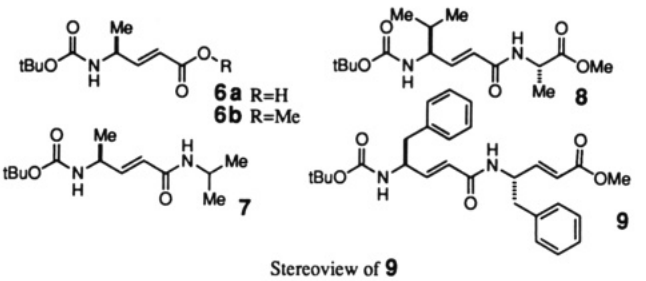


Figure 2. Vinylogous polypeptides can adopt artiparallel sheet secondary structure.



Stereoview of **9**

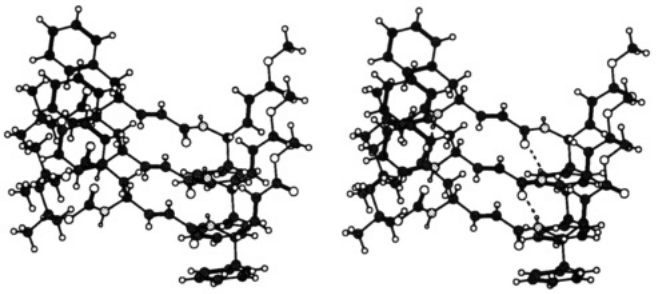


Figure 3. Vinylogous polypeptides can adopt parallel sheet secondary structure.

(2) Note that vinylogous polypeptides do not contain peptide isosteres (ref 2a); they have hydrogen-bonding donor and acceptor groups spaced in a way that is distinct from polypeptides or polypeptides that contain isosteric replacement of the peptide moiety. Vinylogous polypeptides are conceptually related to hexose-DNA (ref 2b), in that a systematic structural alteration has been provided to the repeating unit. (a) Goodman, M.; Chorev, M. *Acc. Chem. Res.* **1979**, *12*, 1–7. (b) Eschenmoser, A. *Nachr. Chem., Tech. Lab.* **1991**, *39* (7/8), 795.

(3) *N*-Boc amino acids were converted to their aldehydes via their Weinreb methoxamides (ref 3a–c) (HN(Me)OMe, DCC, CH_2Cl_2, 78–99%; $LiAlH_4$, THF, 84–94%). Homologations were performed with $Ph_3P{=}CHCO_2Me$ (CH_2Cl_2, 69–89% from Weinreb methoxamide) or $Ph_3P{=}CMeCO_2Et$ (CH_2Cl_2, 86–92% from Weinreb methoxamide). Amide couplings were achieved by treatment of amine (TFA, CH_2Cl_2 or 3 N HCl, MeOH) and carboxylic acid (LiOH, MeOH:H_2O = 3:1) components (1:1) with either DCC (1.05 equiv)/HOBT (1.05 equiv) or BOP (1.20 equiv) in CH_2Cl_2 (58–92%). (a) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815–3818. (b) Fehrentz, J.; Castro, B. *Synthesis* **1983**, 676–678. (c) Lubell, W. D.; Rapoport, H. *J. Am. Chem. Soc.* **1987**, *109*, 236–239.

[†] Harvard University.
[‡] Cornell University.

(1) (a) Pauling, L.; Corey, R. B. *Proc. Natl. Acad. Sci. U.S.A.* **1951**, *37*, 205–211. (b) Pauling, L.; Corey, R. B. *Proc. Natl. Acad. Sci. U.S.A.* **1951**, *37*, 729–740.

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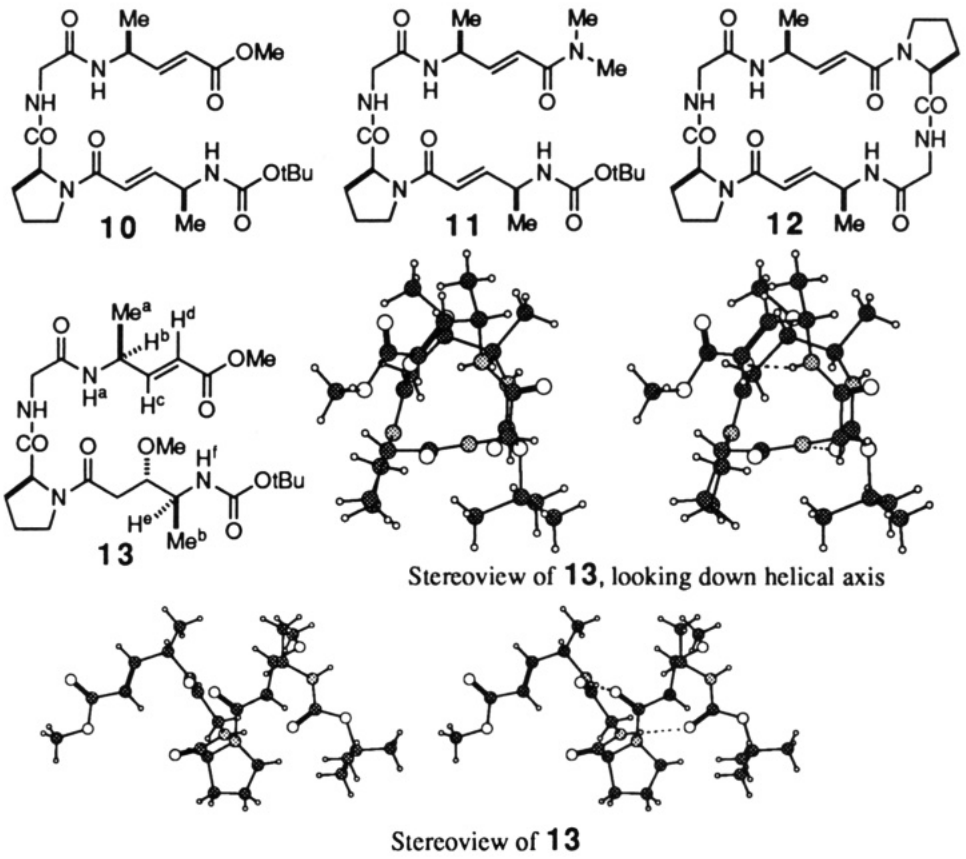

Figure 4. Vinylogous polypeptides can adopt a hairpin turn and a novel helical sheet secondary structure.

of X-ray crystallography and ^{1}H NMR spectroscopy.

In order to restrict rotation of the β,γ-carbon–carbon bond (vinylogous Ψ) of vinylogous polypeptides in a manner that would favor extended, sheetlike conformations, we first examined systems with an α-Me substituent at the vinylogous peptide unit (Figure 2). Considerations of allylic strain ($A^{1,3}$) led to the expectation that the γ-hydrogen would lie in the plane of the enamide (vinylogous $\Psi \approx 120°$). The crystal structures of **3–5** revealed this local conformational preference and the anticipated s-cis conformation of the enamide.[4] A two-stranded, antiparallel sheet is found in the crystal packing of the di(vinylogous)peptide **3** (Figure 2). However, the α-methyl substituent appears to prevent the formation of higher order sheets, as evidenced in the crystal packing of the tri(vinylogous)peptides **4** and **5** (supplementary material).

To alleviate the intermolecular steric interactions of the α-methyl substituent, a second series of (vinylogous)peptides was synthesized and analyzed by X-ray crystallography (Figure 3). The carboxylic acid **6a** was uniquely found to adopt the s-trans conformation in the solid state, although the s-cis conformation is related in this case by a simple proton shift across the ambident carboxylate. Lacking the $A^{1,3}$-constraint of **3–5**, **6b** crystallized with vinylogous $\Psi = -96.8$ and was found to pack without a highly ordered, secondary structure (supplementary material). Simply changing the oxygen of the ester (**6b**) to the NH of an amide (**7–9**) resulted in (vinylogous)peptides that are organized in long stacks of parallel sheets (see **9**, Figure 3; the homologous structures of **7** and **8** are provided in the supplementary material). Apparently, the increased tendency of the amide unit to engage in hydrogen bonding drives the vinylogous Ψ value back to that observed in the sterically constrained systems **3–5**. The factors controlling the directionality of the sheet (antiparallel in **3–5**, parallel in **7–9**) have not yet been defined.

To favor an antiparallel sheet alignment, we examined the influence of a Pro-Gly dipeptide insert. In proteins, this dipeptide element is often found in type II β-turns, although it is known that such turns are rarely found in antiparallel β hairpins.[5] The universal right-handed twist of two-stranded antiparallel sheets is incompatible with the twist of either type I or type II tight turns. Nevertheless, it seemed likely that the (*E*)-alkenyl spacer of (vinylogous)peptides would dampen the right-handed twist constraint. Although the hybrid peptides **10–12** (Figure 4) have proven difficult to crystallize, conformational analyses in solution by NMR have proved illuminating.[6] The ester to amide change in going from **10** to **11** appeared to influence conformation dramatically, as **10** yielded broad signals whereas **11** gave rise to sharp signals strongly shifted downfield. The existence of intramolecular hydrogen bonds involving N- and C-terminal NHs (but not the prolyl-glycyl NH) was suggested by the absence of chemical shift changes with dilution (in contrast to the prolyl-glycyl-NH, which steadily shifted from δ 7.2 to 6.8 upon dilution from 0.28 to 0.07 M (four increments)). A likely explanation is that **11** adopts an antiparallel sheet conformation with a tight turn at the prolyl-glycyl unit. The cyclic hybrid peptide **12** exhibited further downfield shifts in its ^{1}H NMR spectra, especially the β-H of the enamide (δ 7.5 vs 6.9 and 6.8 in **11**). This is consistent with the presence of transannular hydrogen bonds, imposed by the ring constraint. Compound **13**[7] exhibited a ^{1}H NMR spectrum that was strikingly different from those of **10–12**. Notably, the prolyl-glycyl NH was shifted downfield (δ 8.4 vs 7.0 and 6.8 in **11** and **12**, respectively) and did not change chemical shift upon dilution. The long-range NOEs observed with **13**[8] (Figure 4) are consistent with a novel helical solution conformation. Indeed, **13** adopts a heretofore unobserved helical conformation in the solid state, involving two hydrogen bonds, one each in a 10- and 12-membered (including H) "ring". The helix is seen to be related

(4) A search of the CSD for the substructure NC(=O)C=C yielded 16 relevant examples. In each case, the enamide adopts the s-cis geometry.

(5) Sibada, B. L.; Thornton, J. M. *Nature* **1985**, *316*, 170–173.

(6) Selected NMR spectra are provided in the supplementary material.

(7) **13** was isolated as a minor side product in a reaction leading to **10**. A stereospecific Michael addition of methanol occurs during the course of saponification.

(8) The following NOE were observed: Me^a to H^e, 2.5%; Me^a to H^f, 1.9%; Me^b to H^a, 2.8%; Me^b to H^b, 4.2%; Me^b to H^c, 1.4%; Me^b to H^d, 1.0%.

to the 3^{10}-helix of normal peptides, but contains a bulge at the methoxyethyl insert and is C-capped with a type I like β-turn element at the Pro-Gly linkage.[9]

In conclusion, simple, prototype vinylogous polypeptides are seen to be rich in secondary structure. These would appear to be a promising new class of polypeptide-like substances with altered backbones. It will be interesting to determine the receptor-binding properties of these potential ligands. Indeed, the following communication illustrates a naturally occurring vinylogous polypeptide that functions as a high affinity ligand.

Acknowledgment. Support of this research by the AIDS Initiative of the National Institute of General Medical Sciences (GM-44993) is gratefully acknowledged. M.H. thanks Ube Industries, Ltd., for support as a visiting scientist. We are especially grateful to Soroosh Shambayati, whose insights and suggestions were influential throughout this investigation.

Supplementary Material Available: ^{1}NMR spectra (500 MHz) of **10–13**, stereoviews of **4**, **6b**, **7**, and **8**, and tables of crystal data, atomic coordinates, isotropic and anisotropic displacement coefficients, and bond lengths and angles for **3**, **4**, **6b**, **7–9**, and **13** (62 pages). Ordering information is given on any current masthead page.

(9) We note that the β-oxo γ-amino acid (statine-like) moiety is a common structural element in many natural products of biological significance, including statine, dolastatine 10, and didemnin B.

Reassignment of Stereochemistry and Total Synthesis of the Thrombin Inhibitor Cyclotheonamide B

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Modern methods of molecular and structural biology provide excellent opportunities to characterize the interactions between natural products and their cellular receptors.[1] In the process, much can be learned about cellular pathways sensitive to the natural products.[2] Marine sponges have been a rich source of natural products whose influences on cellular function have proved especially illuminating. Examples include okadaic acid,[3] the microcystins,[4] and calyculin[5] that, together with the bacterial natural products FK506 and cyclosporin A,[6] have revealed the significant role of soluble protein phosphatases in signal transduction pathways.[7] More recently, a family of cyclic peptides obtained from the marine sponge genus *Theonella*[8,9] had been characterized that appear to be promising candidates for structural and mechanistic investigations. Of these, the cyclotheonamides[10] attracted our attention for two main reasons. First, it was exciting to discover, in a natural product, a residue we had thus far considered nonnatural but whose synthesis and conformational properties we had studied in some detail. Vinylogous tyrosine (V-Tyr) belongs to the larger class of vinylogous amino acids that can form polymers of regular secondary structure.[11] Second, the presence of an α-keto amide moiety was provocative and strongly suggestive of a mechanism of action for these low molecular weight[12] inhibitors of a protease of the blood coagulation cascade, thrombin (see below). As a first step toward elucidating the structural basis for thrombin–cyclotheonamide complexation, we now report the total synthesis of cyclotheonamide B (CyB) and the modification of the previously reported stereostructure.

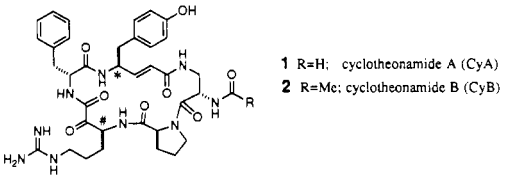
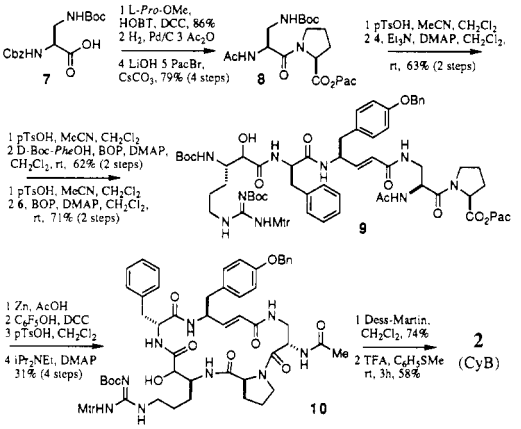


Figure 1. Revised stereostructures of the cyclotheonamides.

Scheme I



In the early phase of our studies, we developed syntheses of both the *R* and *S* stereoisomers at the Arg-like residue (see # in Figure 1; this site was not defined in the original studies) of the proposed structure of CyB (having the proposed *R* stereochemistry at the V-Tyr residue (*S* is shown); see *), using reaction sequences analogous to that shown in Scheme I. The spectral properties of our synthetic samples, however, differed significantly from those of natural CyB kindly provided by Professor Fusetani.[10] We then proposed an alternative stereostructure in Figure 1, containing the *S* stereochemistry at the V-Tyr residue, upon considering the potential pitfalls in the earlier degradative studies[9] and our analyses of NMR spectra from the synthetic and natural samples. The *S* stereochemistry of the Arg-like residue followed from the potent inhibition of thrombin by the *R*(*),*S*(#) synthetic isomer[13] and our speculation concerning thrombin inhibition. (The α-keto group of the cyclotheonamides may function as an electrophilic mimic of the ArgX scissile amide bond of thrombin substrates.) This stereochemical reassignment was confirmed by a synthesis of CyB described below.

L-Proline methyl ester and the protected aminoserine **7**, which was readily synthesized according to the Izumiya procedure,[14] were coupled with DCC/HOBT to yield a dipeptide that was acetylated at its N-terminus (formylation would be required for the synthesis of CyA **1**) and alkylated at its C-terminus with phenacyl (Pac) bromide (Scheme I). Three consecutive amide couplings in the C → N direction converted **8** into the seco-CyB precursor **9**. The

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(4) Dilip de Silva, E.; Williams, D. E.; Anderson, R. J.; Klix, H.; Holmes, C. F. B.; Allen, T. M. *Tetrahedron Lett.* **1992**, *33*, 1561–1564.
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