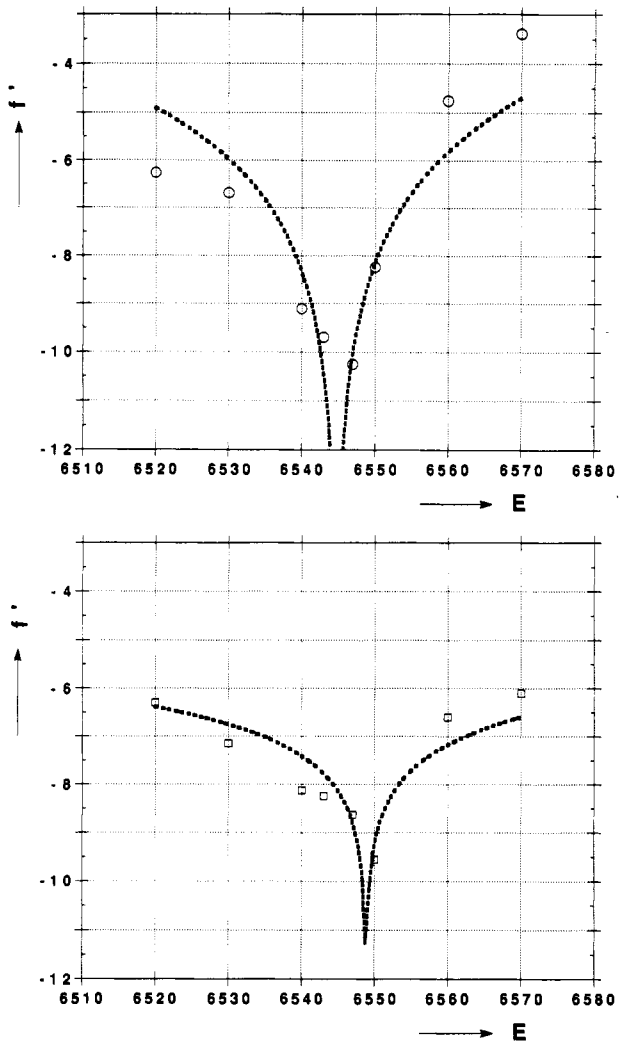



**Figure 3.** Curve fit to $f'$ values of Mn(III) (top) and Mn(IV) (bottom).

real part ($f'$) of the anomalous scattering factors of the two resonating atoms, other structural parameters being kept fixed at the full data set values. Results are shown in Figure 2. The smooth variation of $f'$ indicates that its change with energy is quite well determined. This is confirmed by the reproducibility of $f'$ values in two different experimental runs. Examination shows the Mn(IV) minimum to be at several electronvolts above that for Mn(III). Two curve-fitting methods have been tested to obtain quantitative results. In the first, the *triangle method*, a downward pointing V described by

$$f' = f'_0 + |E - E_0|\delta \quad (1)$$

is fitted to the central six points of each curve, where the variable parameters $f'_0$ and $E_0$ are respectively the $f'$ value and the energy at the minimum, and $\delta$ is the slope.

In the second method, the expression

$$f' = \frac{g_k}{x^2} \ln |x^2 - 1| + \Delta \quad (2)$$

based on an empirical equation given by James,[9] is fitted to all eight points. Here the parameter $g_k$ is the oscillator strength, and $x = E/E_0$. $\Delta$ is a parameter added to the James equation to allow a vertical shift of $f'$. Though neither fit reproduces the data points exceedingly well due to the empirical nature of the curves and neglect of fine structure (Figures 2 and 3 and Table I), the methods agree quite well on the magnitude of the shift of about 4 eV. This result is in agreement with the 3.2-eV difference in

(9) James, R. W. *The Optical Principles of the Diffraction of X-rays*; London: G. Bell and Sons, Ltd.: London, 1954; p 149.

**Table I.** $E_0$ Values from Fitting Procedure

| | $E_0$ (eV) | |
|---|---|---|
| | triangle fit | curve fit |
| Mn(III) | 6543.8 (10) | 6544.8 (10) |
| Mn(IV) | 6547.5 (26) | 6548.8 (24) |
| $E_0$[Mn(IV)] − $E_0$[Mn(III)] | 3.7 | 4.0 |

**Table II.** 1s Binding Energies from an All-Electron Calculation of the $(\mu\text{-}O_2)(Mn(NH_3)_4)_2$ Ion

| | |
|---|---|
| Mn(III) | −240.9647 au |
| Mn(IV) | −241.0814 au |
| $E_0$[Mn(IV)] − $E_0$[Mn(III)] | 0.1167 au = 3.17 eV |

binding energies obtained in our all-electron large basis set ab-initio calculation of the $(\mu\text{-}O_2)(Mn(NH_3)_4)_2$ analogue (Table II). This calculation also yielded a near IR electronic transition of 10020 $cm^{-1}$ compared with the value of ≈830 nm (=12048 $cm^{-1}$) reported for the parent complex.[7]

Clearly Mn atoms of different valency can be distinguished in a careful experiment. This study shows that direct, site-specific information on the valence of atoms in molecular complexes can be obtained by resonance diffraction.

**Acknowledgment.** We thank Prof. Palenik for a set of unpublished coordinates of the perchlorate complex. Support by the National Science Foundation (CHE9021069) is gratefully acknowledged. A.F.-J. is supported through a fellowship from the Danish Science Foundation. The SUNY X3 beamline at NSLS is funded by the Division of Basic Energy Sciences of the U.S. Department of Energy (DEFG0291ER45231). The National Synchrotron Light Source is supported by the U.S. Department of Energy, Division of Materials Sciences and Division of Chemical Sciences.

**Supplementary Material Available:** $f'$ values as a function of the photon energy (1 page). Ordering information is given on any current masthead page.

## Diastereoselectivity in the Amine-Directed Hydrocarboxylation

Marie E. Krafft,*[1] Xiang Y. Yu, Stephen E. Milczanowski, and Karen D. Donnelly

*Department of Chemistry*
*The Florida State University*
*Tallahassee, Florida 32306-3006*

*Received September 5, 1991*

We have previously described a regioselective directed hydrometalation/carbonylation[2] of bidentate olefinic amine Rh(I) complexes (eq 1: R′, R″ = H; R = H, alkyl).[3-5] Our continued studies probed the diastereofacial selectivity of the process as influenced by the existence of stereogenic centers on the tether connecting the alkene and amine (eq 1: R = R′ = R″ = alkyl, H). We now report that the amine-directed hydrocarboxylation

(1) Fellow of the A. P. Sloan Foundation, 1989–1993. Camille and Henry Dreyfus Teacher–Scholar, 1989–1994.

(2) For leading references, see: Pearson, A. J. *Metallo-Organic Chemistry*; Wiley: New York, 1985. Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987. Davies, S. G. *Organotransition Metal Chemistry: Applications to Organic Synthesis*; Pergamon: Oxford, 1982. *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI Press: Greenwich, CT, 1989; Vol. 1. Zhou, J.-Q.; Alper, H. *J. Org. Chem.* **1992**, *57*, 3328. Ojima, I.; Zhang, Z. *Organometallics* **1990**, *9*, 3122. Ojima, I.; Clos, N.; Bastos, C. *Tetrahedron* **1989**, *45*, 6901.

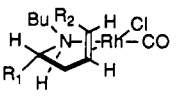
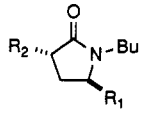
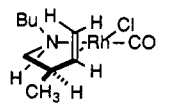
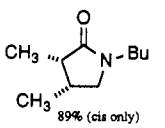
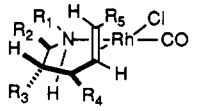
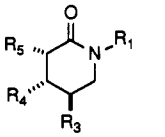
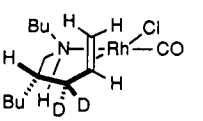
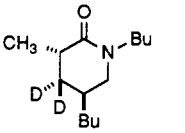
(3) Krafft, M. E.; Wilson, L. J.; Onan, K. D. *Tetrahedron Lett.* **1989**, *29*, 6421.

(4) Krafft, M. E.; Wilson, L. J.; Onan, K. D. *Organometallics* **1988**, *7*, 2528.

(5) Krafft, M. E. *Tetrahedron Lett.* **1989**, *30*, 539.

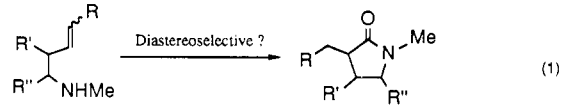
0002-7863/92/1514-9215$03.00/0 

**Table I**

| entry | | Rh(I) complex[a] | | lactam (yield)[a] | |
|---|---|---|---|---|---|
| 1 | 1 |  | $R_1$=Ph, $R_2$=H, |  | 86% |
| 2 | 2 | | $R_1$=$CH_3$, $R_2$=H | | 85% (14 : 1)[b] |
| 3 | 3 | | $R_1$=$CH_3$, $R_2$=Et | | 95% (8 : 1) |
| 10 | | | $R_1$=Ph, $R_2$=$CH_3$ | | 90% (trans only) |
| 11 | | | $R_1$=$CH_3$, $R_2$=$CH_3$ | | 40% (trans only) |
| 12 | | | $R_1$=$CH_3$, $R_2$=Pr | | 86% (+3%cis) |
| 4 | 4 |  | |  | 89% (cis only) |
| 5 | 5 |  | $R_1$=Bu, $R_2$=$R_4$=$R_5$=H, $R_3$=$CH_3$ |  | 90% |
| 6 | 6 | | $R_1$=Pr, $R_2$=$R_3$=H, $R_4$=Ph, $R_5$=$CH_3$ | | 81% (6:1) |
| 7 | 7 | | $R_1$=Bu, $R_2$=$CH_3$, $R_3$=$R_4$=$R_5$=H | | 85% (7.5:1) |
| 8 | 8 | | $R_1$=H, $R_2$=Ph, $R_3$=$R_4$=$R_5$=H | | 86% |
| 14 | | | $R_1$=Bu, $R_4$=H, $R_3$=$R_5$=$CH_3$ (trans only) | | 90% |
| 15 | | | $R_1$=Pr, $R_3$=H, $R_4$=Ph, $R_5$=Et (cis only) | | 25% |
| | | | | | ...[c] |
| | | | | | ...[c] |
| 9 | 9 |  | |  | 80% |
| 16 | | | | | 71% (trans only) |

[a] Isolated yields. Reactions run at −78 °C. [b] Ratio determined by $^1$H NMR. [c] See text for explanation.

is a highly diastereofacially selective process as a result of the selectivity in the Rh(I) complex forming step.




(1)

Lactams **10–15** (Table I) were formed diastereoselectively by hydrometalation/carbonylation[3] [HCl, $P(OMe)_3$, $CH_2Cl_2$, −78 °C; MeOH, $P(OMe)_3$, −78 °C to room temperature] of the corresponding Rh(I) complexes **1–6**.[4,6] Homoallylic amine complexes **1–4** reacted cleanly to give substituted butyrolactams. The exclusive formation of the cis-disubstituted lactam **13** suggests that, once formed, the product does not equilibrate under the reaction conditions. Bishomoallylic amine complexes **5–7** yielded only the unexpected butyrolactams when the reaction was performed at 0 °C; however, at −78 °C complexes **5**, **6**, and **9** yielded only the desired valerolactams. Substitution at the amino methylene carbon of a bishomoallylic amine led to the formation of complexes **7** and **8** with a high degree of selectivity. However, complex **7** gave only a butyrolactam (1-butyl-3-ethyl-5-methyl-2-pyrrolidinone, 80%) when the reaction was carried out at 0 °C, and neither the butyrolactam nor the desired valerolactam was found when the reaction was performed at −78 °C. Reactions with complex **8** were less satisfactory, and no lactams or any other recognizable products were obtained.

The overall hydrocarboxylation process is believed to proceed in two steps—hydrometalation in a syn fashion[5] followed by carbonylation with retention of configuration at the migrating center.[10] Reaction of the allylic dideuterio complex **9** gave lactam **16** with no evidence of deuterium scrambling. This result strongly suggests that the hydrometalation under these conditions does not proceed through the intermediacy of π-allyl intermediates. The diastereoselectivity associated with the lactam formation should therefore be a direct result of the stereochemistry of the Rh(I) complex and the strong π-facial bias associated with the Rh(I) complex formation.[7,8] In bidentate complexes **1–7** and **9**, the saturated alkylamino group is syn (as determined by $^1$H NOE studies) to the terminus of the alkene, whose C–C bond prefers to lie orthogonal to the plane of the square planar complex.[4,9,10,12]

The Rh(I) complexes are apparently formed in an equilibrium process[13] and are evidently in equilibrium in solution at ambient temperature. Complex **4** was isolated as a 4:1 mixture of isomers from the reaction of $[(CO)_2RhCl]_2$ with (2-methylbut-3-enyl)-butylamine. Recrystallization of the mixture yielded a 10:1 mixture of diastereomers. Upon standing in $CDCl_3$ overnight, the complexes equilibrated back to a 4:1 mixture.

Insight into the selectivity of complex formation can be obtained by evaluating steric interactions in the possible diastereomeric Rh(I) complexes. The four possible diastereomeric products for complexes **1** or **2** are illustrated in Scheme I. Potential steric interactions in the Rh(I) complexes that may be responsible for the observed selectivity are noted on structures **A–D**.

Interestingly, the 4:1 mixture of diastereomeric Rh(I) complexes **4** listed as entry 4 in the table gave rise to an 89% yield of a single lactam **13** (cis-disubstituted). This could be a result of equilibration of the complexes at low temperature (−78 °C) although the rate of equilibration would be expected to be significantly slower than at ambient temperature. But, this result may also suggest that the identity of the minor isomer is the other Rh(I) complex that can lead to the cis-disubstituted lactam **13** (analogous to those complexes illustrated in the scheme for **1** and **2**, but with a different substitution pattern).

We have shown that the amine-directed[14] rhodium-promoted

(6) The Rh(I) complexes were formed by the reaction of the corresponding alkenylamine with $[(CO)_2RhCl]_2$ in hexane/$CH_2Cl_2$ at ambient temperature. The structure of the major Rh(I) complex is depicted in the table. The structure was determined by $^1$H NOE experiments. We were never able to obtain the minor isomer in pure form; thus its identity remains unknown. Assignment of the stereochemistry at the Rh center was based on analogy to an X-ray of a similar Rh(I) complex; see ref 4.

(7) During the course of our work, a diastereoselective hydrocarboxylation of an alkenyl amino ester was reported: Zahn, I.; Wagner, B.; Polborn, K.; Beck, W. *J. Organomet. Chem.* **1990**, *394*, 601.

(8) A high-pressure, rhodium acetate catalyzed hydroformylation of analogous olefinic amine substrates was recently reported (1:1 mixtures of diastereomers were obtained). Anastasiou, D.; Jackson, W. R. *Tetrahedron Lett.* **1990**, *31*, 4795.

(9) Krafft, M. E.; Milczanowski, S. E. Unpublished results.

(10) Hoffmann, R.; Thorn, D. L. *J. Am. Chem. Soc.* **1978**, *100*, 2079. Hoffmann, R.; Stockis, A. *J. Am. Chem. Soc.* **1980**, *102*, 2952. Rakowsky, M. H.; Woolcock, J. C.; Wright, L. L.; Green, D. B.; Rettig, M. F.; Wing, R. M. *Organometallics* **1987**, *6*, 1211. Albright, T. A.; Hoffmann, R.; Thibeault, J. C.; Thorn, D. L. *J. Am. Chem. Soc.* **1979**, *101*, 3801. Doherty, N. M.; Bercaw, J. E. *J. Am. Chem. Soc.* **1985**, *107*, 2670. Schunn, R. A. *Inorg. Chem.* **1970**, *9*, 2567. Berke, H.; Hoffmann, R. *J. Am. Chem. Soc.* **1978**, *100*, 7224.

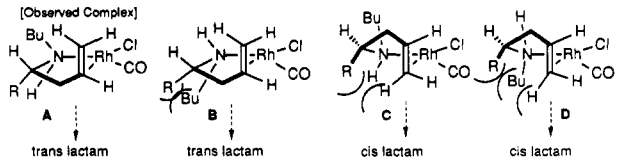
(11) Vallarino, L. M.; Sheargold, S. W. *Inorg. Chim. Acta* **1979**, *36*, 243.

(12) For discussions on the mechanism of ligand exchange, see: Atwood, J. D. *Inorganic and Organometallic Reaction Mechanisms*; Brooks/Cole: Monterey, CA, 1985. Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987. Heck, R. F. *Organotransition Metal Chemistry, A Mechanistic Approach*; Academic: New York, 1974.

(13) The olefinic amine Rh(I) complexes readily exchange with free olefinic amines in solution.

(14) For some other examples of heteroatom-directed transition metal mediated reactions, see: Eisch, J. J. *J. Organomet. Chem.* **1980**, *200*, 101. Prasad, J. V. N.; Pillai, C. N. *J. Organomet. Chem.* **1983**, *259*, 1. Holton, R. A. *J. Am. Chem. Soc.* **1977**, *99*, 8083. Holton, R. A.; Kjonaas, R. A. *J. Am. Chem. Soc.* **1977**, *99*, 4177. Hauser, F. M.; Ellenberger, S. R.; Clardy, J. C.; Bass, L. S. *J. Am. Chem. Soc.* **1984**, *106*, 2458. Johnson, C. R.; Barbachyn, M. R. *J. Am. Chem. Soc.* **1984**, *106*, 2459. Preston, S. A.; Cupertino, D. C.; Palma-Ramirez, P.; Cole-Hamilton, D. J. *J. Chem. Soc., Chem. Commun.* **1986**, 977. Burke, S. D.; Cobb, J. E. *Tetrahedron Lett.* **1986**, *27*, 4237. Evans, D. A.; Morrissey, M. M.; Dow, R. L. *Tetrahedron Lett.* **1985**, *26*, 6005. Crabtree, R. H.; Davis, M. W. *J. Org. Chem.* **1986**, *51*, 2655 and references cited therein. Rao, A. S. *Tetrahedron* **1983**, *39*, 2323. Krafft, M. E. *J. Am. Chem. Soc.* **1988**, *110*, 968. Thompson, H. W.; McPherson, E. *J. Org. Chem.* **1977**, *42*, 3350. Thompson, H. W.; Shah, N. V. *J. Org. Chem.* **1983**, *48*, 1325. Tamao, K.; Nakagawa, Y.; Arai, H.; Higuchi, N.; Ito, Y. *J. Am. Chem. Soc.* **1988**, *110*, 3712. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1985; Vol. 5. Behrens, C. H.; Sharpless, K. B. *Aldrichimica Acta* **1983**, *16*, 67. Anastasiou, D.; Jackson, W. R. *Tetrahedron Lett.* **1990**, *31*, 4795. Jackson, W. R.; Perlmutter, P.; Tasdelen, E. E. *Tetrahedron Lett.* **1990**, *31*, 2461. Hanessian, S.; Thavonekham, B.; DeHoff, B. *J. Org. Chem.* **1989**, *54*, 5831. Zhang, W.-Y.; Jakiela, D.; Maul, A.; Knors, C.; Lauher, J. W.; Helquist, P.; Enders, D. *J. Am. Chem. Soc.* **1988**, *110*, 4652. Klang, J. A.; Collum, D. B. *Organometallics* **1988**, *7*, 1532. Park, J.; Pedersen, S. F. *J. Org. Chem.* **1990**, *55*, 5924.

**Scheme I**




alkene hydrocarboxylation is a highly diastereofacially selective process due to the selectivity inherent in the ligand exchange process and the syn nature of the hydrometalation. Further studies are in progress, and these results will be reported in due course.

**Acknowledgment.** We acknowledge partial support of this work from the National Institutes of Health, the National Science Foundation, the Sloan Foundation, and the Camille and Henry Dreyfus Foundation. The Johnson Matthey Company is gratefully acknowledged for generous loans of rhodium trichloride. We thank Professor Will Rees (FSU) for helpful discussions.

**Supplementary Material Available:** Listings of spectral data for Rh(I) complexes **3–7** and **9** and lactams **11–13** and **16** (9 pages). Ordering information is given on any current masthead page.

## Nonpeptidal Peptidomimetics with a β-D-Glucose Scaffolding. A Partial Somatostatin Agonist Bearing a Close Structural Relationship to a Potent, Selective Substance P Antagonist

Ralph Hirschmann,* K. C. Nicolaou,*,† Sherrie Pietranico,‡ Joseph Salvino,§ Ellen M. Leahy,∥ Paul A. Sprengeler, George Furst, and Amos B. Smith, III*

*Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104*

Catherine D. Strader,* Margaret A. Cascieri, and Marialuisa R. Candelore

*Department of Molecular Pharmacology and Biochemistry, Merck Research Laboratories Rahway, New Jersey 07065*

Cindy Donaldson and Wylie Vale*

*The Salk Institute, La Jolla, California 92037*

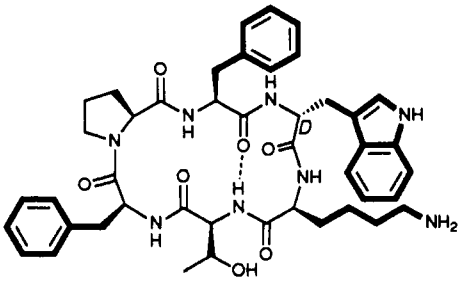
Laurie Maechler*

*Panlabs, Inc., 11804 North Creek Parkway South Bothell, Washington 98011*

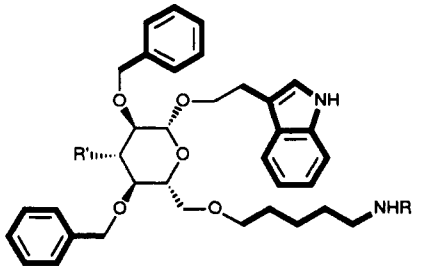
*Received July 29, 1992*

We report herein that the use of β-D-glucose as a scaffold for the synthesis of nonpeptidal peptidomimetics[1] has revealed three noteworthy findings: (1) a designed nonpeptidal peptidomimetic is recognized by its receptor at low concentrations as an agonist; (2) at higher concentrations this compound becomes the first known antagonist of somatostatin (SRIF); and (3) a completely unexpected change in biological profile results from a seemingly minor structural modification.

The design and synthesis of β-D-glucose-based nonpeptide mimetics of the potent cyclic hexapeptide SRIF agonist (**I**)[2,3] were previously reported.[4] It was found that **II** and **III** completely displaced [$^{125}$I]-CGP 23996 from SRIF receptors on membranes from cerebral cortex, pituitary, and AtT-20 cells with $IC_{50}$'s of 10 and 1.3 μM, respectively.[5] Sugars **II** and **III** also bound weakly to the $\beta_2$-adrenergic receptor. Subsequent analysis has now shown that **III** is a $\beta_2$-adrenergic antagonist with an $IC_{50}$ of 3 μM.



**I** (L-363,301)



**II** R = H, R' = OBn
**III** R = R = H
**IV** R = Ac, R' = OBn

We now report the striking observation that in a functional assay **III** inhibits GRF-induced growth hormone (GH) release by cultured rat anterior pituitary cells[6] with an $IC_{50}$ of 3 μM, i.e., **III** is an SRIF agonist at its endocrine receptor. That **III** can act as an SRIF agonist strongly suggests that the binding is specific and that the SRIF receptor recognizes the designed **III** as an SRIF mimetic. This agonism runs counter to the prevailing opinion that designed peptidomimetics with novel scaffolding are unlikely to achieve the degree of fit at the endocrine receptor required for agonism.[7] The maximal level of inhibition (found at 50 μM) was only about half that seen with an optimal level of SRIF, suggesting that **III** is a partial agonist. Indeed at higher concentrations, **III** antagonized SRIF-induced receptor activation. That **III** is the first compound, peptidal or nonpeptidal, to display a long-sought antagonism at the SRIF receptor is at least as noteworthy as the above agonism.

We have now found that **II** and **III** display a higher affinity to the substance P (SP) receptor, with $IC_{50}$'s of 0.12 and 0.18 μM, respectively. Remarkably, the *N*-acetyl derivative **IV**[9] binds to

† Present address: The Scripps Research Institute, La Jolla, CA 92037, and University of California, San Diego, La Jolla, CA 92093.
‡ Present address: Hoffmann-LaRoche, Inc., Nutley, NJ 07110.
§ Present address: Sterling Winthrop, Inc., Great Valley, PA 19355.
∥ Present address: 4059 Minuet Circle, El Sobrante, CA 94803.

(1) Farmer, P. S. In *Drug Design*; Ariëns, E. J., Ed.; Academic: New York, 1980; Vol X, p 119. Spatola, A. F. In *Chemistry and Biochemistry of Amino Acids, Peptides, and Proteins*; Weinstein, B., Ed.; Marcel Dekker: New York, 1983; p 267. See also: Freidinger, R. M. *TIPS Rev.* **1989**, *10*, 270. Sherman, D. B.; Spatola, A. F. *J. Am. Chem. Soc.* **1990**, *112*, 433. Hirschmann, R. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1278 and references cited therein.

(2) Veber, D. F.; Freidinger, R. M.; Perlow, D. S.; Paleveda, W. J.; Holly, F. W.; Strachan, R. G.; Nutt, R. F.; Arrison, B. H.; Homnick, C.; Randall, W. C.; Glitzer, M. S.; Saperstein, R.; Hirschmann, R. *Nature* **1981**, *292*, 55.

(3) We are indebted to Dr. R. M. Freidinger for making available to us the coordinates of the solution structure of cyclic hexapeptide **I**.

(4) Nicolaou, K. C.; Salvino, J. M.; Raynor, K.; Pietranico, S.; Reisine, T.; Freidinger, R. M.; Hirschmann, R. In *Peptides: Chemistry, Structure and Biology*; Rivier, J. E., Marshall, G. R.; Escom: Leiden, The Netherlands, 1990; p 881.

(5) G. L. Olson (Olson, G. L.; Cheung, H.-C.; Voss, M. E.; Hill, D. E.; Kahn, M.; Madison, V. S.; Cook, C. M.; Sepinwall, J.; Vincent, G. In *Proc. Biotechol. (USA)*; Conference Management Corporation: Norwalk, CT, 1989; p S.348) reported at about the same time the conceptually related design of a TRH mimetic which exhibits oral activity in animal models of cognitive dysfunction, but does not bind to the high-affinity endocrine TRH receptor (Olson, G. L. Personal communication to R.H.).

(6) Rivier, J.; Spiess, J.; Thornes, M.; Vale, W. *Nature* **1982**, *300*, 276.

(7) To our knowledge there is only one prior design for an endocrine receptor of a nonpeptidal peptidomimetic agonist with novel scaffolding (Bélanger, P. C.; Dufresne, C. *Can. J. Chem.* **1986**, *64*, 1514).

0002-7863/92/1514-9217$03.00/0 