Pergamon

Tetrahedron 56 (2000) 9773–9779

TETRAHEDRON

# Asymmetric Acylation Reactions Catalyzed by Conformationally Biased Octapeptides

Elizabeth R. Jarvo, Melissa M. Vasbinder and Scott J. Miller*

*Department of Chemistry, Merkert Chemistry Center, Boston College, Chestnut Hill, MA 02467-3860, USA*

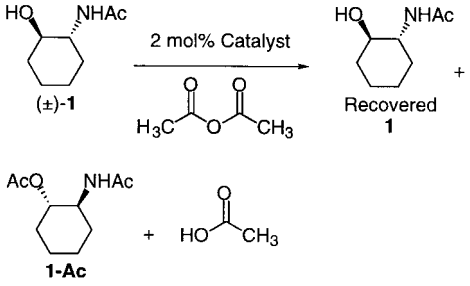
Received 26 April 2000; accepted 31 July 2000

**Abstract**—Octapeptides capable of adopting β-hairpin conformations have been found to function as efficient catalysts for the kinetic resolution of certain racemic secondary alcohols. Parallel solid phase synthesis of a series of peptides with the common feature of the D-Pro-Gly sequence at the turn region ($i+3$ to $i+4$) was carried out to yield a family of octapeptide catalysts. The peptides were then screened for their efficiency in a number of enantioselective acylation reactions. 

## Introduction

Small peptides that promote asymmetric reactions are emerging as efficient catalysts for asymmetric synthesis. Pioneering examples include the work of Inoue[1] and Lipton,[2] who showed that simple diketopiperazines are effective catalysts for asymmetric cyanohydrin formation and the Strecker reaction, respectively. Given the prominent role of enzymes in the field of asymmetric organic synthesis,[3] and the emerging applications of catalytic antibodies in organic synthesis,[4] the study of low molecular weight peptides that catalyze asymmetric reactions stands as an interfacial area of research. On the one hand, enzymes and antibodies are typically highly complex in their structures; complex scaffolds and binding domains are often at the heart of the high selectivities they exhibit. Yet, relatively simple structures such as diketopiperazines, and even single amino acids such as proline,[5] can provide levels of enantioselectivity that are competitive in particular cases.[6] The structural diversity available with peptide-based catalysts, even within short peptide sequences, makes this class of molecules particularly promising for the development of a broad range of asymmetric reactions. As part of a program targeted at discovery of efficient asymmetric catalysts, we have been studying low molecular weight peptides that catalyze the kinetic resolutions of racemic secondary alcohols.[7]

In our initial studies, we established that incorporation of alkylimidazoles resulted in peptides that are highly active as catalysts for acylation of secondary alcohols (e.g., **1**) when acetic anhydride is used as the acylating agent (Eq. (1)). In particular, imidazolyl alanine (IA, see structures **2** and **3**) and π-(Me)-histidine (Pmh, see structure **4**) were utilized as α-amino acid analogs of the well-known acylation catalysts of the *N*-alkylimidazole class.[8]




(1)

Specifically, we found that incorporation of these amino acids into short peptides of defined secondary structure led to a class of asymmetric catalysts that enable kinetic resolution of certain alcohols (Fig. 1).[9] Whereas catalyst **2**, devoid of any secondary structure, is ineffective as an asymmetric catalyst, peptide **3**, which exists as a type II β-turn, catalyzes the kinetic resolution of substrate **1** with a $k_{rel}$ of 17.[10] Exchange of IA for Pmh, in combination with swapping L-Pro for D-Pro in the $i+1$ position of the peptide led to the minimal β-hairpin **4**.[11] This conformationally rigidified peptide affords an improved kinetic resolution of substrate **1** with a $k_{rel}$ of 28.

Elaboration of the β-hairpin to an octapeptide (**5**, Fig. 2) resulted in a highly selective catalyst, exhibiting $k_{rel}$=51. In stark contrast to catalyst **5**, however, stands octapeptide catalyst **6**, which exhibits a modest $k_{rel}$ of 7 in the same kinetic resolution. The only difference between peptides **5** and **6** is that peptide **5** bears a D-Pro residue in the $i+3$ position, whereas **6** possesses an L-Pro residue. This seemingly subtle variation has profound consequences. Peptide **5** affords a sharp $^1$H NMR spectrum, consistent

*Keywords*: octapeptides; β-hairpin conformation; enantioselective acylation; kinetic resolution.

* Corresponding author. Tel.: +(617)-552-3620; fax: +(617)-552-2705; e-mail: scott.miller.1@bc.edu

0040–4020/00/$ - see front matter 
PII: S0040-4020(00)00884-X

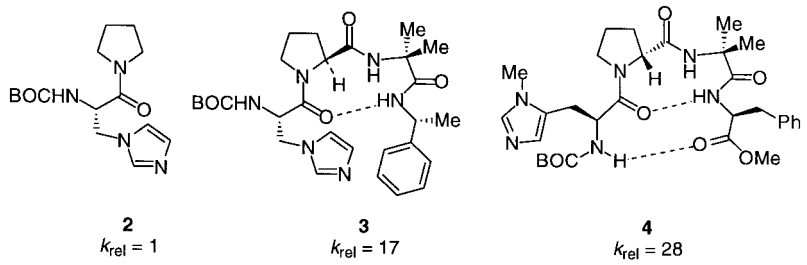



**Figure 1.**

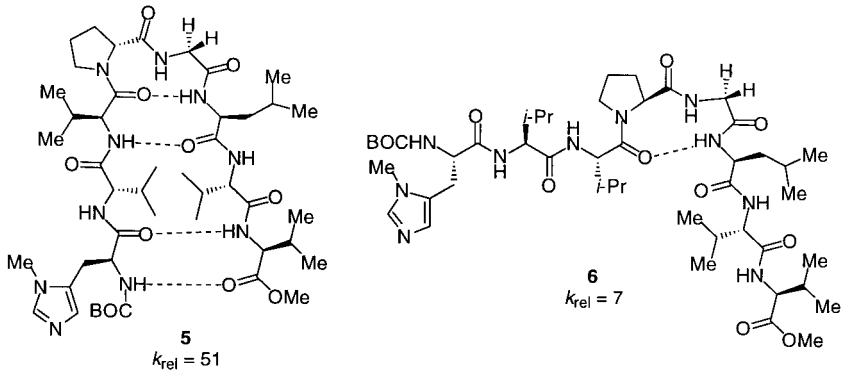
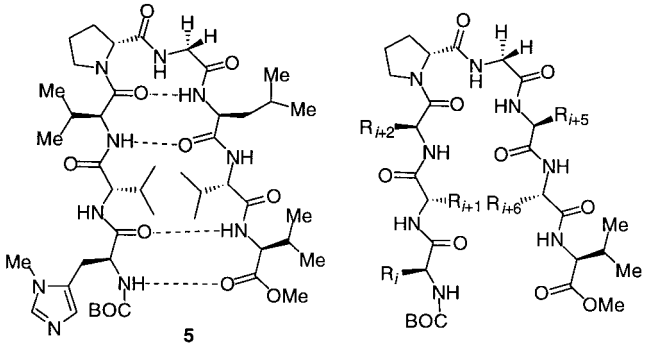



**Figure 2.**

with a unique conformation in solution. Peptide **6**, with the L-Pro residue, exhibits a $^1$H NMR spectrum with broad peaks, consistent with multiple conformations or aggregation. These observations are in accord with prior findings in the peptide design field.[12] In particular, the D-Pro-Gly sequence has been shown to be a highly efficient nucleator of β-hairpin structures. In contrast, the L-Pro-Gly sequence tends to result in peptides that exhibit conformational heterogeneity and aggregation phenomena in organic solvent.[13] In the context of the asymmetric catalysis, the exchange of the D-Pro (catalyst **5**) for the L-Pro (catalyst **6**) results in a change in $k_{rel}$ from 51 to 7. This drastic change in selectivity stems from a single stereochemical perturbation. A single stereogenic center (D-Pro vs L-Pro) thirteen atoms removed from the key catalytic site (the Pmh τ-Nitrogen) drastically alters the peptide conformation. Indeed, this remote asymmetric center has significant consequences for the enantioselectivity afforded by these otherwise similar catalysts.




**Peptide Catalysts (Position of Pmh in Bold)**

**5**, BOC-**Pmh**-Val-Val-D-Pro-Gly-Leu-Val-Val-OMe

**7**, BOC-Val-**Pmh**-Val-D-Pro-Gly-Leu-Val-Val-OMe

**8**, BOC-Val-Val-**Pmh**-D-Pro-Gly-Leu-Val-Val-OMe

**9**, BOC-Val-Val-Val-D-Pro-Gly-**Pmh**-Val-Val-OMe

**10**, BOC-Val-Val-Val-D-Pro-Gly-Leu-**Pmh**-Val-OMe

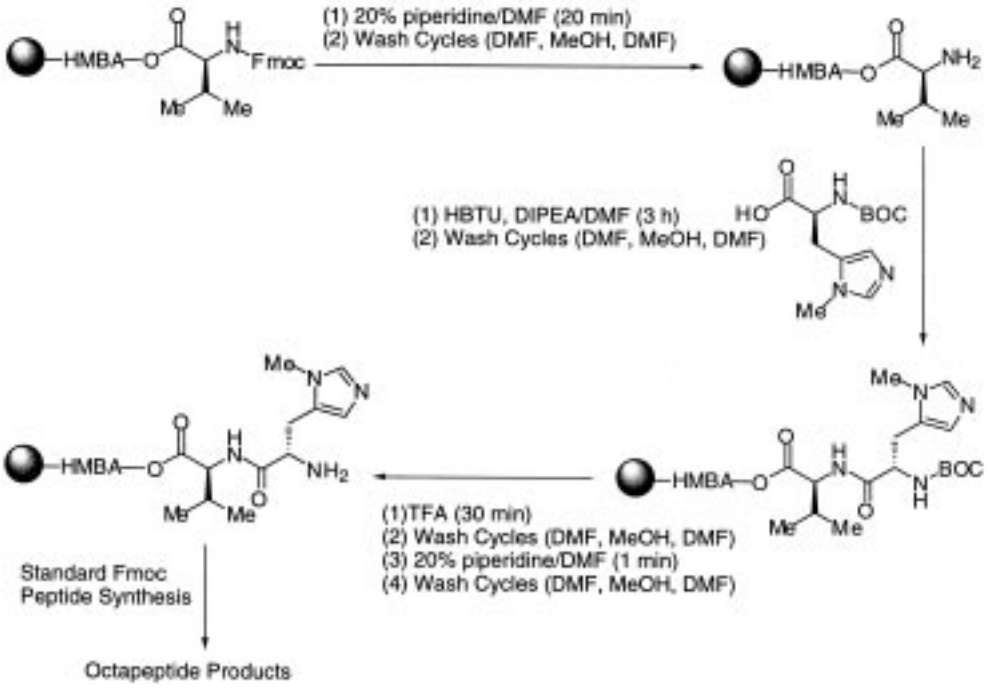
**Figure 3.** Peptide catalysts (position of Pmh in bold): **5**, BOC-**Pmh**-Val-Val-D-Pro-Gly-Leu-Val-Val-OMe; **7**, BOC-Val-**Pmh**-Val-D-Pro-Gly-Leu-Val-Val-OMe; **8**, BOC-Val-Val-**Pmh**-D-Pro-Gly-Leu-Val-Val-OMe; **9**, BOC-Val-Val-Val-D-Pro-Gly-**Pmh**-Val-Val-OMe; **10**, BOC-Val-Val-Val-D-Pro-Gly-Leu-**Pmh**-Val-OMe.

With the catalytic residue so remote from this key asymmetric center, we set out to determine whether or not peptides with the His-derived alkylimidazole more proximate to the D-Pro residue might afford more selective catalysts. Accordingly, we prepared octapeptides **7**, **8**, **9** and **10**. As shown in Fig. 3, the targeted peptides were intended to favor the β-hairpin conformation by retaining the D-Pro-Gly sequence in the turn region. Incorporation of the Pmh residue at the $i+1$ (**7**), $i+2$ (**8**), $i+5$ (**9**), and $i+6$ (**10**) positions was designed to provide a collection of peptides with representative spacing of the catalytic heterocycle about the octapeptide scaffold. All other positions in the sequence were held constant.

## Results and Discussion

### Synthesis of peptides

The peptides were prepared by standard solid phase peptide synthesis (SPPS). In this particular instance, a parallel synthesis was undertaken using the Fmoc method employing

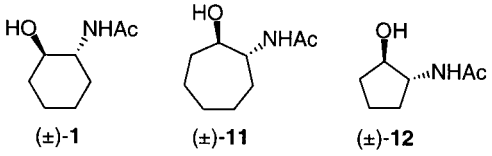



**Scheme 1.**

polystyrene resin beads functionalized with the HMBA linker.[14] One modification was necessary due to the potential lability of the Fmoc group in the presence of the basic Pmh residue (Scheme 1). For the Pmh residue,[15] the BOC group was employed for *N*-terminal protection. Following standard coupling conditions, the resins were treated with TFA for 30 min. Wash cycles (5X) were then carried out with DMF, MeOH and DMF. A critical additional wash with 20% piperidine/DMF was then carried out for one minute to ensure complete neutralization of TFA. After standard wash cycles, typical Fmoc SPPS was resumed. With this method, each of the peptides was obtained. All new peptides were purified by reverse phase HPLC, and characterized by the usual methods. (See Experimental, below.)

## Kinetic resolutions

Catalytic peptides **5**, **7**, **8**, **9** and **10** were each screened for their ability to catalyze kinetic resolutions of three substrates. We had previously shown that peptide **5** functions best with acetamide-functionalized substrates such as **1**. In addition, we explored resolutions of seven- and five-membered ring substrates **11** and **12** below.




In previous studies, we had shown that octapeptide **5** was an excellent catalyst for the resolution of substrate **1** ($k_{rel}$=51). While the highest selectivity was observed for the cyclohexene-derived substrate, efficient resolutions were also observed with seven-membered ring **11** ($k_{rel}$=15) and the five-membered ring **12** ($k_{rel}$=27). The results from evaluation of the new catalysts with these substrates are summarized in Table 1. In all cases, catalysts were examined under the optimized conditions previously reported (1–2.5 mol % catalyst; $PhCH_3$, 25°C, 5.9 mM in substrate).

Screening of octapeptide **7**, with the Pmh residue in the $i+1$ position, reveals that this catalyst affords sufficient enantioselectivity, although it is less selective than the original peptide **5** for each of the *trans*-1,2-hydroxyacetamides. The six- and five-membered ring substrates (**1** and **12**) exhibit similar $k_{rel}$ values of 8 and 9, respectively (entries 4 and 6). The seven-membered ring substrate **11** participates

**Table 1.** Selectivities for cyclic *trans*-1,2-hydroxyacetamides in kinetic resolutions with octapeptide catalysts **5**, **7**, **8**, **9** and **10** (reactions were conducted with 1–2.5 mol% catalyst, 5.9 mM in substrate, $PhCH_3$ solvent) at 25°C. Conversions and enantioselectivities were measured by chiral GLC (Chiraldex GTA). See Experimental for details)

| Entry | Catalyst | Racemic substrate | Conversion | $k_{rel}$ ($k_{RR}/k_{SS}$) |
|---|---|---|---|---|
| 1 | Octapeptide **5** | **1** | 50 | 51:1 |
| 2 | | **11** | 45 | 15:1 |
| 3 | | **12** | 49 | 27:1 |
| 4 | Octapeptide **7** | **1** | 52 | **1:8** |
| 5 | | **11** | 55 | **1:12** |
| 6 | | **12** | 49 | **1:9** |
| 7 | Octapeptide **8** | **1** | 55 | 14:1 |
| 8 | | **11** | 49 | 6:1 |
| 9 | | **12** | 49 | 4:1 |
| 10 | Octapeptide **9** | **1** | 47 | 2:1 |
| 11 | | **11** | 48 | 1:1 |
| 12 | | **12** | 52 | 2:1 |
| 13 | Octapeptide **10** | **1** | 55 | **1:2** |
| 14 | | **11** | 55 | **1:2** |
| 15 | | **12** | 60 | **1:1** |

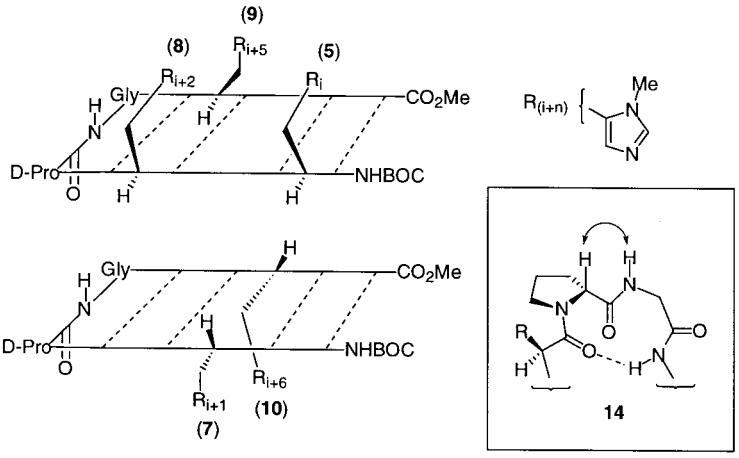



**Figure 4.** Disposition of Pmh-side chain in the β-hairpin scaffold for peptide catalysts **5**, **7**, **8**, **9** and **10**.

in a slightly more selective reaction with this catalyst ($k_{rel}$=12, entry 5). It is of particular interest that this catalyst selectively acylates the *opposite* enantiomer of substrate relative to peptide **5**. (The (*S*,*S*)-enantiomer is preferentially acylated, vide infra.) Octapeptide **8** (Pmh in the $i$+2 position) also provides substantial levels of enantioselection, although it is still a less selective catalyst than **5**. Nevertheless, substrate **1** is processed with $k_{rel}$=14 (entry 7). Substrates **11** and **12** also exhibit appreciable $k_{rel}$ values (**11**, $k_{rel}$=6, entry 8; **12**, $k_{rel}$=4, entry 9). In these cases, the sense of enantioselectivity parallels that exhibited by catalyst **5** (acylation of (*R*,*R*)-enantiomer preferred).

Octapeptides **9** and **10** proved to be less selective catalysts than peptides **5**, **7**, or **8**. Octapeptide **9** (Pmh in the $i$+5 position) effects the kinetic resolution of both substrates **1** and **12** with a modest $k_{rel}$=2 (entries 10 and 12), but was nonselective towards **11** (entry 11). As with peptides **5** and **8**, peptide **9** catalyzes the preferential acylation of the (*R*,*R*)-enantiomer of *trans*-1,2-hydroxyacetamides **1** and **12**. Peptide **10** (Pmh in the $i$+6 position) affords modest selectivity factors for substrates **1** and **11** (**1**, $k_{rel}$=2, entry 13; **11**, $k_{rel}$=2, entry 14), but is nonselective towards substrate **12** ($k_{rel}$=1, entry 15). However, as with peptide **7**, opposite enantiospecificity is observed, with the (*S*,*S*)-enantiomers of substrates **1** and **11** undergoing preferential acylation with this peptide catalyst.

While it is difficult to craft a definitive explanation for the results presented above, an intriguing trend does emerge. Although detailed conformational analyses must be carried out to allow a complete determination of the dominant conformation in solution for each peptide, if one assumes the preference of the β-hairpin structure in the reactive conformations of the peptides, the following conclusions can be drawn. For peptides **5**, **8** and **9**, the catalytic imidazole is disposed on the same face of the β-hairpin structure (top face, as drawn in Fig. 4). Notably, each of these peptides affords the same sense of induction with the *trans*-1,2-hydroxyacetamides, exhibiting $k_{rel}$ values where the (*R*,*R*)-enantiomer is the faster reacting of the two enantiomers. In contrast, peptide catalysts **7** and **10** localize the catalytic imidazole on the opposite face (bottom face, as drawn in Fig. 4.) Significantly, these two peptides exhibit opposite enantioselectivity, where the (*S*,*S*)-enantiomer is the faster reacting isomer.

Prior studies of the solution conformations of several D-Pro-Gly octapeptide β-hairpins have shown that in the local turn region, the D-Pro-Gly linkage adopts the local conformation exhibited by structure **14**.[12,13] Specifically, the Gly NH is often disposed *syn* to the D-Pro-Cα-H, indicative of a Type II' turn at this juncture. Indeed, nOe analysis of catalyst **5** is also consistent with this conformation. Although it is not possible at this time to propose a final explanation for the opposite enantioselectivities exhibited by these peptides, it does appear that the orientation of the substrate on the 'top' or 'bottom' face of the β-hairpin plane could be a critical determinant of the sense of enantioselection with these substrates. Future studies with peptide based catalysts, and related peptidomimetics will help in determining the relevance of these interactions.

## Conclusion

In summary, we have reported new octapeptide catalysts that effect enantioselective acylation reactions. It is clear that peptides armed with imidazole functional groups provide the diversity necessary for classes of acylation catalysts with different selectivity profiles. Such catalysts could prove valuable for development of detailed structure–selectivity profiles that shed light on the mechanisms by which these catalysts work. Also, applications with the most selective of the catalysts represents an area for future work.

## Experimental

### General procedures

Proton NMR spectra were recorded on Varian 400 or 300 spectrometers. Proton chemical shifts are reported in ppm ($\delta$) relative to internal tetramethylsilane (TMS, $\delta$ 0.0). Data are reported as follows: chemical shift (multiplicity [singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m)], coupling constants [Hz], integration). Carbon NMR spectra

were recorded on Varian 400 (100 MHz) spectrometer with complete proton decoupling. Carbon chemical shifts are reported in ppm ($\delta$) relative to TMS with the respective solvent resonance as the internal standard ($CDCl_3$, $\delta$ 77.0). NMR data were collected at 25°C, unless otherwise indicated. Infrared spectra were obtained on a Perkin–Elmer Spectrum 1000 spectrometer. Analytical thin-layer chromatography (TLC) was performed using Silica Gel 60 F254 pre-coated plates (0.25 mm thickness). TLC $R_f$ values are reported. Visualization was accomplished by irradiation with a UV lamp and/or staining with $KMnO_4$ or Cerium ammonium molybdenate (CAM) solutions. Flash column chromatography was performed using Silica Gel 60A (40 micron) from Scientific Adsorbents Inc. Optical rotations were recorded on a Perkin–Elmer-241 digital polarimeter at the sodium D line (path length 100 mm). Elemental analyses were performed by Robertson Microlit (Madison, NJ). High resolution mass spectra were obtained at the Mass Spectrometry Facilities either of the University of Illinois (Urbana-Champaign, IL), Harvard University (Cambridge, MA), or Boston College (Chestnut Hill, MA). The method of ionization is given in parentheses.

Analytical GC was performed on a Hewlett-Packard 6890 employing a flame ionization detector and the column specified in the individual experimental. Analytical and preparative HPLC were performed on a Rainin SD-200 chromatograph equipped with a single wavelength UV detector (214 nm).

All reactions were carried out under an argon atmosphere employing oven- and flame-dried glassware. All solvents were distilled from appropriate drying agents prior to use. Acetic anhydride was distilled prior to use and stored in a Schlenk tube for no more than 1 week. *trans*-2-Acetamidocyclohexanol **1** and *trans*-2-acetamidocyclopentanol **12** were prepared according to the method of Hawkins.[16] *trans*-2-Acetamidocycloheptanol **11** was prepared according to the method of Honig[17] and Jacobsen.[18]

## Standard conditions for kinetic resolutions

The optimized conditions for the kinetic resolutions are exemplified by the following experimental protocol for the resolution of alcohol (±)-**1**. Alcohol (±)-**1** (64.2 mg, 0.408 mmol) was dissolved in 69.1 mL of toluene. This stock solution was distributed in 9.5 mL aliquots to reaction vessels containing peptides **5**, **7**, **8**, **9** and **10** (0.001 mmol in 0.1 mL $CH_2Cl_2$). Acetic anhydride (25 μL, 0.265 mmol) was then introduced. The reactions were allowed to stir at room temperature. Aliquots were removed, quenched with methanol and directly assayed by chiral GC analysis as described below.

**Data for diacetate 1-Ac.** $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 5.79 (broad d, $J$=6.7 Hz, 1H), 4.60 (dt, $J$=10.8, 4.4 Hz, 1H), 3.81 (dddd, $J$=12.0, 10.8, 6.7, 4.4 Hz, 1H), 1.99 (s, 3H), 1.87 (s, 3H), 2.19–1.10 (m, 8H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 171.8, 169.6, 74.6, 52.7, 32.0, 31.0, 24.1, 24.0, 23.3, 21.1; IR (film, $cm^{-1}$) 3287, 3102, 2935, 2864, 1737, 1647; TLC $R_f$ 0.29 (EtOAc); Anal. Calcd for $C_{10}H_{17}N_1O_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.49; H, 8.64; N, 6.92; Exact mass calcd for $[C_{10}H_{17}N_1O_3+H]+$ requires $m/z$ 200.1287. Found 200.1285 (CI).

**Assay of enantiomeric purity.** Enantiomers of starting material **1** and product **1-Ac** were separated by chiral GC employing a 30 m Chiraldex G-TA column (Alltech). Conditions: Oven Temperature Ramp: Step Gradient: Initial temperature (run time 0–14 min)=135°C. Final temperature (run time 14–24 min)=150°C. Flow rate=60 psi. Retention Times: **1-Ac**: $R_{t(R,R)}$=12.0 min; $R_{t(S,S)}$=12.8 min. Retention Time: **1**: $R_{t(R,R)}$=18.9 min; $R_{t(S,S)}$=19.9 min.

**Proof of absolute stereochemistry.** Optically enriched diacetate **1-Ac** (400 mg, 2.00 mmol) was dissolved in 2N HCl solution (60 mL), and the resulting solution was heated at reflux for 3 h. The solution was then filtered and concentrated to afford 295 mg (97%) of a white powder. The sample was precipitated from $MeOH/CH_2Cl_2$ to afford *trans*-2-aminocyclohexanol·HCl salt, spectra of which were identical to those described in the lit.[18] Measurement of the optical rotation and comparison to the literature showed the sample to be of the (*S*,*S*)-configuration. $[\alpha]_D$=+33.2 (*1.1*, EtOH); (Literature for (*S*,*S*)-*trans*-2-aminocyclohexanol·HCl: $[\alpha]_D$=+37.0 (*1.1*, EtOH)).

**Data for diacetate 11-Ac.** $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 5.65 (broad d, $J$=6.8 Hz, 1H), 4.81(m, 1H), 4.00 (dq, $J$=3.5, 9.0 Hz, 1H), 2.03 (s, 3H), 1.91 (s, 3H), 1.86–1.46 (m, 10H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 171.6, 169.3, 77.4, 55.3, 31.5, 31.4, 27.6, 24.0, 23.5, 22.5, 21.3; IR (film, $cm^{-1}$) 3273, 3080, 2928, 2869, 1741, 1653; TLC $R_f$ 0.31 (EtOAc); Anal. Calcd for $C_{11}H_{18}N_1O_3$: C, 61.95; H, 8.98; N, 6.57. Found: C, 61.64; H, 8.97; N, 6.32; Exact mass calcd for $[C_{11}H_{19}N_1O_3+H]+$ requires $m/z$ 214.1443. Found 214.1452 (CI).

**Assay of enantiomeric purity.** Enantiomers of product **11-Ac** were separated by chiral GC employing a 30m Chiraldex G-TA column (Alltech). Conversion was calculated using a Response Factor obtained for tetradecane/product as follows: Response Factor=(mmol **11-Ac**)(area tetradecane)/(mmol tetradecane)(area **11-Ac**)=1.602. Conditions: Oven Temperature 135°C. Flow rate=60 psi. Retention Times: **11-Ac**: $R_{t(R,R)}$=19.7 min; $R_{t(S,S)}$=20.5 min. Retention Time: tetradecane: 2.0 min.

**Proof of absolute stereochemistry.** Product **11-Ac** was hydrolyzed in a fashion analogous to that employed for **1-Ac** (page SI-5). The hydrochloride salt was converted to its corresponding free base through $NaHCO_3$ extraction for direct comparison to the literature. $[\alpha]_D$=+19.8 (*1.0*, EtOH); (Literature for (*S*,*S*)-*trans*-2-aminocycloheptanol: $[\alpha]_D$=+17.0 (*1.0*, EtOH)[19]).

**Data for Diacetate 12-Ac.** $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 6.14 (broad s, 1H), 4.97 (q, $J$=6.2 Hz, 1H), 4.15 (quintet, $J$=7.3 Hz, 1H), 2.23 (m, 1H), 2.05 (overlapping m and s, 4H), 1.96 (s, 3H), 1.72 (m, 3H), 1.43 (m, 1H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 171.3, 170.1, 79.0, 56.1, 30.4, 29.5, 23.2, 21.1, 20.6; IR (film, $cm^{-1}$) 3278, 3076, 2967, 2875, 1735, 1652; TLC $R_f$ 0.30 (5% $MeOH/CH_2Cl_2$); Anal. Calcd for $C_9H_{15}N_1O_3$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.44;

H, 8.30; N, 7.60; Exact mass calcd for $[C_9H_{15}N_1O_3+H]+$ requires *m/z* 186.1130. Found 186.1130 (FAB).

**Assay of enantiomeric purity.** Enantiomers of starting material **12** and product **12-Ac** were separated by chiral GC employing a 30 m Chiraldex G-TA column (Alltech). Conditions: Oven Temperature 150°C. Flow rate=60 psi. Retention Times: **12-Ac**: $R_{t(R,R)}$=5.2 min, $R_{t(S,S)}$=6.3 min. Retention Time: **12**: $R_{t(R,R)}$=7.5 min, $R_{t(S,S)}$=10.1 min.

**Proof of absolute stereochemistry.** Product **12-Ac** was hydrolyzed in a fashion analogous to that employed for **1-Ac**. Measurement of the optical rotation and comparison to the literature showed the sample to be of the (*R*,*R*)-configuration. $[\alpha]_D=-13.3$ (*0.77*, EtOH); Literature for (*S*,*S*)-*trans*-2-aminocyclopentanol·HCl: $[\alpha]_D=+29.7$ (*1.95*, EtOH).[18]

## Peptide synthesis

Peptides were synthesized on the solid support using commercially available HMBA-AM polystyrene resin (Novabiochem). The carboxy terminus amino acid was loaded as the *N*-α-Fmoc derivative via conventional symmetrical anhydride loading protocols. Couplings were performed using 4 equiv. amino acid derivative, 4 equiv. HBTU, and 8 equiv. Hunig's base in DMF, for 3 h. FMOC-deprotections were performed using 20% piperidine in DMF for 20 min (to minimize diketopiperazine formation, dipeptides were deprotected using 50% piperidine in DMF for 5 min). BOC-deprotections were performed using TFA for 30 min, followed by a free base wash with 20% piperidine in DMF for one minute. Peptides were cleaved from solid support using a mixture of MeOH:DMF:$NEt_3$ (9:1:1) for 4 d. Peptides were purified using reverse phase HPLC techniques. Preparative HPLC was performed using a reverse phase RP-18 X Terra (Waters) column, eluting with 65–75% methanol in water, at a flow rate of 6 mL/min. The purity was checked by analytical HPLC under similar conditions, and the peptides were characterized by $^1$H NMR and electrospray mass spectrometry.

## Data for peptides

**Peptide 5.** $^1$H NMR ($CDCl_3$, 400 MHz) δ 7.84 (broad m, 3H), 7.34 (broad s, 2H), 7.20 (broad d, *J*=8.2 Hz, 1H), 6.75 (broad s, 1H), 6.58 (broad d, *J*=9.2 Hz, 1H), 5.39 (broad d, *J*=7.7 Hz, 1H), 4.66–4.52 (m, 4H), 4.44–4.34 (m, 3H), 4.11 (dd, *J*=6.8, 16.8 Hz, 1H), 3.84–3.78 (m, 2H), 3.72 (m, 1H), 3.70 (s, 3H), 3.56 (s, 3H), 3.04–2.90 (m, 2H), 2.22–1.98 (m, 8H), 1.80–1.53 (m, 3H), 1.40 (s, 9H), 0.97–0.85 (m, 30H); TLC $R_f$ 0.18 (8% MeOH/$CH_2Cl_2$); Exact mass calcd for $[C_{46}H_{78}N_{10}O_{11}+H]+$ requires *m/z* 947.5930. Found 947.5932 (FAB); Analytical HPLC: Purity of peptide **5** was assayed using a reverse phase RP-18 X Terra (Waters) column. Conditions: isocratic elution with 60% methanol in water, at a flow rate of 0.2 mL/min. Retention time=3.4 min.

**Peptide 7.** $^1$H NMR ($CDCl_3$, 400 MHz) δ 8.45 (d, *J*=8.8 Hz, 1H), 8.22 (d, *J*=8.4 Hz, 1H), 7.79 (broad m, 1H), 7.63 (d, *J*=8.8 Hz, 1H), 7.27 (s, 1H), 6.80 (s, 1H), 6.57 (d, *J*=7.7 Hz, 1H), 6.37 (d, *J*=9.5 Hz, 1H), 5.89 (d, *J*=9.2 Hz, 1H), 5.55 (broad m, 1H), 4.91 (t, *J*=9.5 Hz, 1H), 4.60 (dd, *J*=6.2, 8.8 Hz, 1H), 4.54 (m, 1H), 4.45 (dd, *J*=7.2, 17.0 Hz, 1H), 4.31–4.23 (m, 2H), 3.91 (m, 1H), 3.75 (overlapping s and m, 5H), 3.53 (s, 3H), 3.30 (broad m, 1H), 2.96 (m, 1H), 2.89 (m, 1H), 2.26 (m, 1H), 2.18–2.07 (m, 4H), 1.95 (m, 3H), 1.84–1.68 (m, 2H), 1.51 (m, 1H), 1.43 (s, 9H), 0.94–0.82 (m, 30H); TLC $R_f$ 0.18 (8% MeOH/$CH_2Cl_2$); Exact mass calcd for $[C_{46}H_{78}N_{10}O_{11}+H]+$ requires *m/z* 947.5930. Found 947.5948 (ESI); Analytical HPLC: Purity of peptide **7** was assayed using a reverse phase RP-18 X Terra (Waters) column. Conditions: isocratic elution with 60% methanol in water, at a flow rate of 0.2 mL/min. Retention time=4.7 min.

**Peptide 8.** $^1$H NMR ($CDCl_3$, 400 MHz) δ 8.83 (d, *J*=8.1 Hz, 1H), 8.22 (d, *J*=8.4 Hz, 1H), 7.75 (d, *J*=8.4 Hz, 1H), 7.38 (s, 1H), 7.24 (m, 1H), 6.85 (m, 3H), 5.57 (d, *J*=8.8 Hz, 1H), 4.93 (broad m, 1H), 4.78 (t, *J*=8.4 Hz, 1H), 4.71 (t, *J*=8.8 Hz, 1H), 4.57–4.53 (m, 2H), 4.6 (dd, *J*=5.1, 7.3 Hz, 1H), 4.19 (dd, *J*=7.7, 17.9 Hz, 1H), 3.95 (t, *J*=7.7 Hz, 1H), 3.73 (overlapping s and m, 4H), 3.65 (s, 4H), 3.27 (broad m, 1H), 3.19 (dd, *J*=11.4, 14.2 Hz, 1H), 2.78 (dd, *J*=3.5, 14.4 Hz, 1H), 2.18–1.95 (m, 7H), 1.83 (m, 1H), 1.73 (m, 1H), 1.63 (m, 2H), 1.44 (s, 9H), 0.98–0.86 (m, 30H); TLC $R_f$ 0.21 (8% MeOH/$CH_2Cl_2$); Exact mass calcd for $[C_{46}H_{78}N_{10}O_{11}+H]+$ requires *m/z* 947.5930. Found 947.5911 (ESI); Analytical HPLC: Purity of peptide **8** was assayed using a reverse phase RP-18 X Terra (Waters) column. Conditions: isocratic elution with 60% methanol in water, at a flow rate of 0.2 mL/min. Retention time=4.0 min.

**Peptide 9.** $^1$H NMR ($CDCl_3$, 400 MHz) δ 8.62 (broad s, 1H), 8.36 (d, *J*=7.7 Hz, 1H), 8.03 (broad s, 1H), 7.70 (broad s, 1H), 7.43 (broad s, 1H), 7.05 (broad s, 1H), 6.98 (broad s, 1H), 6.69 (d, *J*=9.5 Hz, 1H), 5.60 (broad d, *J*=9.2 Hz, 1H), 4.76 (m, 2H), 4.67 (t, *J*=9.4 Hz, 1H), 4.56–4.50 (m, 3H), 4.32 (m, 1H), 4.23 (m, 1H), 3.89 (t, *J*=8.4 Hz, 1H), 3.84–3.77 (m, 1H), 3.73 (s, 3H), 3.65 (m, 1H), 3.48 (broad s, 3H), 3.31 (broad m, 1H), 2.86 (broad m, 1H), 2.20–1.90 (m, 9H), 1.41 (s, 9H), 0.99–0.87 (m, 30H); TLC $R_f$ 0.12 (8% MeOH/$CH_2Cl_2$); Exact mass calcd for $[C_{45}H_{76}N_{10}O_{11}+H]+$ requires *m/z* 933.5773. Found 933.5737 (ESI); Analytical HPLC: Purity of peptide **9** was assayed using a reverse phase RP-18 X Terra (Waters) column. Conditions: isocratic elution with 60% methanol in water, at a flow rate of 0.2 mL/min. Retention time=4.0 min.

**Peptide 10.** $^1$H NMR ($CDCl_3$, 400 MHz) δ 8.49 (d, *J*=8.8 Hz, 1H), 7.80 (d, *J*=8.8 Hz, 1H), 7.61 (d, *J*=7.3 Hz, 1H), 7.38 (broad s, 1H), 7.18 (m, 1H), 7.08 (broad m, 1H), 6.82 (broad s, 1H), 6.68 (broad s, 1H), 5.71 (d, *J*=8.4 Hz, 1H), 5.00 (m, 1H), 4.68 (m, 1H), 4.50–4.42 (m, 3H), 4.36 (m, 1H), 3.97–3.91 (m, 2H), 3.87–3.83 (m, 2H), 3.72 (s, 3H), 3.66 (m, 1H) 3.51 (s, 3H), 3.08 (dd, *J*=7.2, 15.7 Hz, 1H), 2.96 (dd, *J*=7.0, 14.6 Hz, 1H) 2.19–1.97 (m, 9H), 1.71–1.65 (m, 2H), 1.45 (s, 9H), 0.92–0.85 (m, 30H); TLC $R_f$ 0.21 (8% MeOH/$CH_2Cl_2$); Exact mass calcd for $[C_{46}H_{78}N_{10}O_{11}+H]+$ requires *m/z* 947.5930. Found 947.5948 (ESI); Analytical HPLC: Purity of peptide **10** was assayed using a reverse phase RP-18 X Terra

(Waters) column. Conditions: isocratic elution with 60% methanol in water, at a flow rate of 0.3 mL/min. Retention time=9.1 min.

## Acknowledgements

This research is supported by the National Science Foundation (CHE-9874963). We are also grateful to the National Institutes of Health for generous support of our research (GM-57595). In addition we thank, DuPont, Eli Lilly, Glaxo-Wellcome and the Merck Chemistry Council for research support. S. J. M. is a Fellow of the Alfred P. Sloan Foundation, a Cottrell Scholar of Research Corporation, and a Camille Dreyfus Teacher–Scholar.

## References

1. Kenzo, T.; Mori, A.; Inoue, S. *J. Org. Chem.* **1990**, *55*, 181–185.
2. Iyer, M. S.; Gigstad, K. M.; Namdev, N. D.; Lipton, M. *J. Am. Chem. Soc.* **1996**, *118*, 4910–4911.
3. For reviews, see: (a) Wong, C.-H.; Whitesides, G. M. *Enzymes in Synthetic Organic Chemistry*; Elsevier: Oxford, 1994. (b) Johnson, C. R. *Acc. Chem. Res.* **1998**, *31*, 333–341 and references therein.
4. For example, see: Sinha, S. C.; Sun, J.; Miller, G.; Barbas III, C. F.; Lerner, R. A. *Org. Lett.* **1999**, *1*, 1623–1626.
5. (a) List, B.; Lerner, R. A.; Barbas, III, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396. (b) Agami, C.; Puchot, C.; Sevestre, H. *Tetrahedron Lett.* **1986**, 1501–1504.
6. For examples of dipeptides that catalyze enantioselective hydrolyses at a micellar interface, see: Cleij, M. C.; Drenth, W.; Nolte, R. J. M. *J. Org. Chem.* **1991**, *56*, 3883–3891.
7. For other representative, nonenzymatic enantioselective nucleophilic catalysts, see: (a) Vedejs, E.; Chen, X. *J. Am. Chem. Soc.* **1996**, *118*, 1809–1810. (b) Vedejs, E.; Daugulis, O. *J. Am. Chem. Soc.* **1999**, *121*, 5813–5814. (c) Tao, B.; Ruble, J. C.; Hoic, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **1999**, *121*, 5091–5092. (d) Fu, G. C. *Acc. Chem. Res.* **2000**, *33*, 412–420, and references therein. (e) Kawabata, T.; Nagato, M.; Takasu, K.; Fuji, K. *J. Am. Chem. Soc.* **1997**, *119*, 3169–3170. (f) Oriyama, T.; Imai, K.; Hosoya, T.; Sano, T. *Tetrahedron Lett.* **1998**, *39*, 397–400. (g) Spivey, A. C.; Fekner, T.; Spey, S. E. *J. Org. Chem.* **2000**, *65*, 3154–3159.
8. (a) Pandit, N. K.; Obaseki, A. O.; Connors, K. A. *Anal. Chem.* **1980**, *52*, 1678–1679. (b) Pandit, N. K.; Connors, K. A. *J. Pharm. Sci.* **1982**, *71*, 485–491.
9. (a) Copeland, G. T.; Jarvo, E. R.; Miller, S. J. *J. Org. Chem.* **1998**, *63*, 6784–6785. (b) Miller, S. J.; Copeland, G. T.; Papaioannou, N.; Horstmann, T. E.; Ruel, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 1629–1630. (c) Jarvo, E. R.; Copeland, G. T.; Papaioannou, N.; Bonitatebus, Jr., P. J.; Miller, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11638–11643.
10. (a) $k_{rel}$=*s*-factor; $k_{rel}$ ($k_{rel}=k_{fast}/k_{slow}$) values were calculated according to the method of Kagan. See: Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249–330. (b) Reaction selectivities and conversions were determined in analogy to the method we reported previously (Ref. 9). See Experimental for details.
11. Haque, T. S.; Little, J. C.; Gellman, S. H. *J. Am. Chem. Soc.* **1996**, *118*, 6975–6985.
12. (a) For a review of the field, see: Gellman, S. H. *Curr. Opin. Chem. Biol.* **1998**, *2*, 717–725. See also: (b) Stanger, H. E.; Gellman, S. H. *J. Am. Chem. Soc.* **1998**, *120*, 4236–4237. (c) Karle, I. L.; Awasthi, S. K.; Balaram, P. *Proc. Natl. Acad. Sci. USA* **1996**, *93*, 8189–8193.
13. Raghothama, S. R.; Awasthi, S. K.; Balaram, P. *J. Chem. Soc., Perkin Trans. 2* **1998**, 137–143.
14. Bodanszky, M. *Principles of Peptide Synthesis*; 2nd Ed.; Springer: Berlin, 1993, pp 38–52.
15. Beyerman, H. C.; Maat, L.; Van Zon, A. *Recl. Trav. Chim. Pays-Bas* **1972**, *91*, 246–250.
16. Hawkins, L. R.; Bannard, R. A. B. *Can J. Chem.* **1958**, *36*, 220.
17. Honig, H.; Seufer-Wasserthal, P. *J. Chem. Soc., Perkin Trans. 1* **1989**, 2341–2345.
18. Schaus, S. E.; Larrow, J. F.; Jacobsen, E. N. *J. Org. Chem.* **1997**, *62*, 4197–4199.
19. Aubé, J.; Wolfe, M. S.; Yantiss, R. K.; Cook, S. M.; Takusagawa, F. *Synth. Commun.* **1992**, *22*, 3003–3012.