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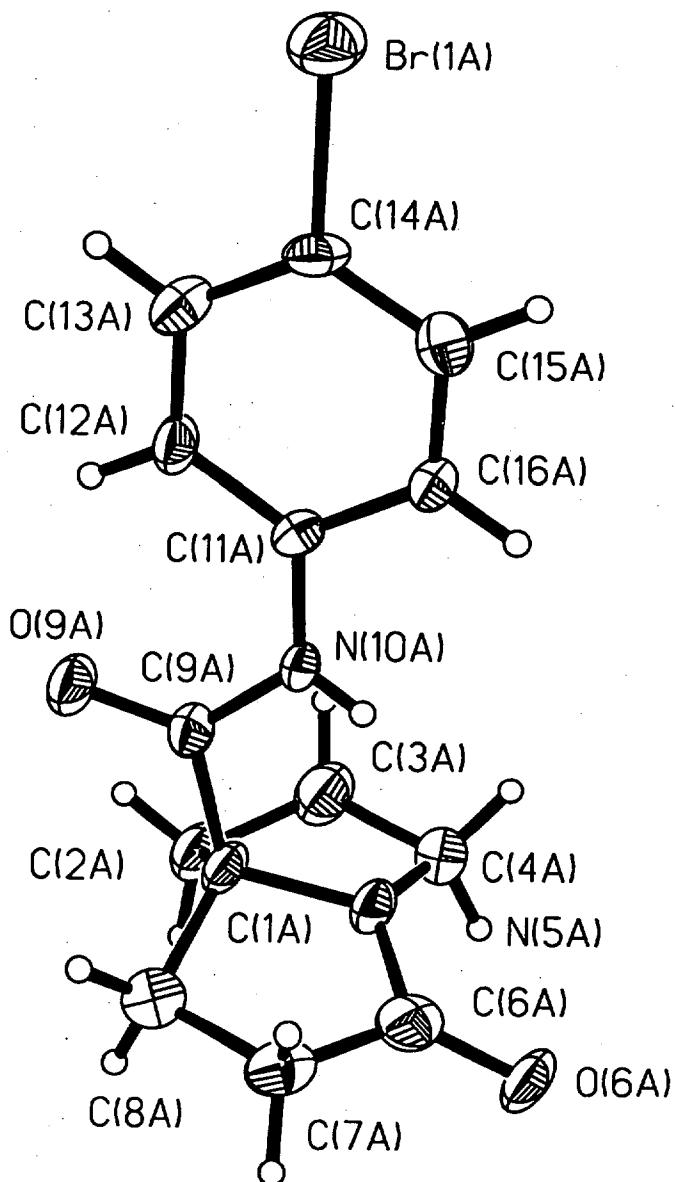
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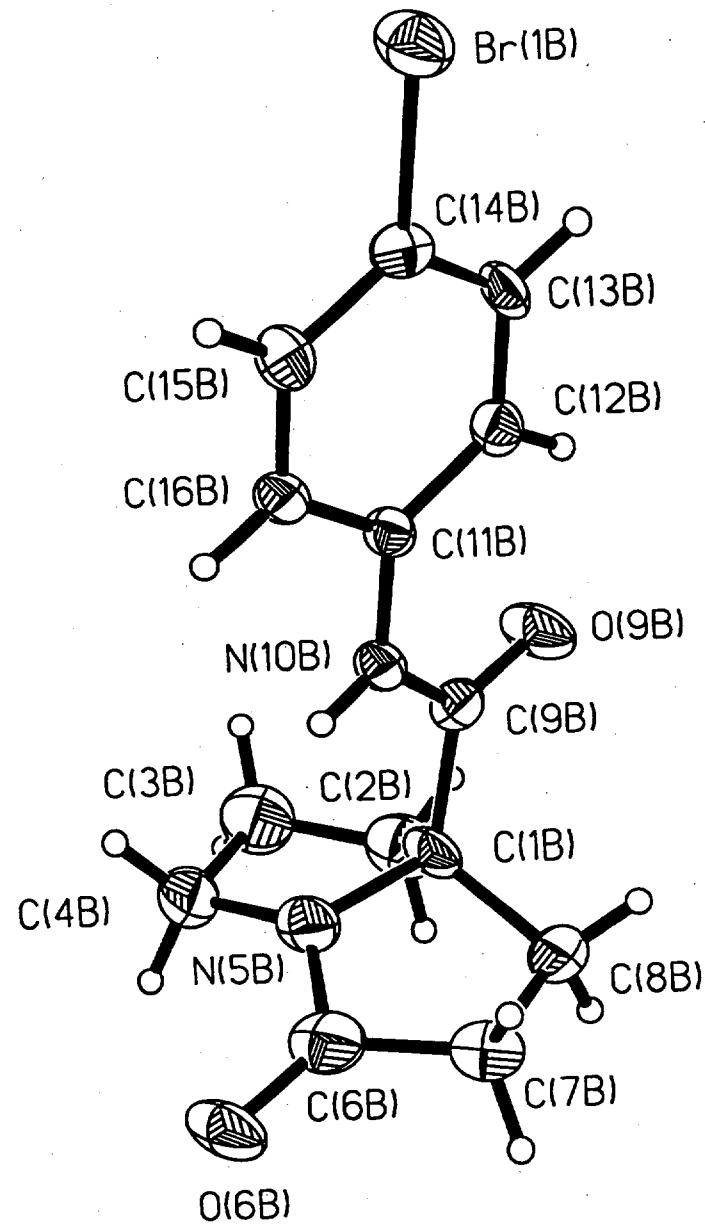
Intramolecular Catalysis of Amide Isomerization: Kinetic Consequences of the  
5-NH--N<sub>a</sub> Hydrogen Bond in Prolyl Peptides

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Supporting Figure 1. Crystal structure of enantiomorph A of locked amide 3d (50% ellipsoids).



**Supporting Figure 2.** Crystal structure of enantiomorph B of locked amide **3d** (50% ellipsoids).

## DATA COLLECTION

173 K

A crystal of the compound was attached to a glass fiber and mounted on the Siemens SMART system for a data collection at ~~293~~(2) K. An initial set of cell constants was calculated from reflections harvested from four sets of 30 frames. These initial sets of frames are oriented such that orthogonal wedges of reciprocal space were surveyed. This produces orientation matrices determined from 111 reflections. Final cell constants are calculated from a set of 5099 strong reflections from the actual data collection. Final cell constants reported in this manner usually are about one order of magnitude better in precision than reported from four-circle diffractometers. Please refer to Table 1 for additional crystal and refinement information.

The data collection technique used for this specimen is generally known as a hemisphere collection. Here a randomly oriented region of reciprocal space is surveyed to the extent of 1.3 hemispheres to a resolution of 0.84 Å. Three major swaths of frames are collected with 0.30° steps in  $\omega$ . This collection strategy provides a high degree of redundancy. The redundant data provide good  $\psi$  input in the event an empirical absorption correction is applied (see Table 1).

## STRUCTURE SOLUTION AND REFINEMENT

The space group  $P2_1/c$  was determined based on systematic absences and intensity statistics.<sup>1</sup> A successful direct-methods solution was calculated which provided most non-hydrogen atoms from the E-map. Several full-matrix least squares / difference Fourier cycles were performed which located the remainder of the non-hydrogen atoms. All non-hydrogen atoms were refined with anisotropic displacement parameters unless stated otherwise. All hydrogen atoms were placed in ideal positions and refined as riding atoms with individual isotropic displacement parameters. The exception to this was the refinement of both amide hydrogens located on N10A and N10B. Since the position was in question these were refined positionally and the isotropic displacement parameter was held at 1.2 times the  $U_{iso}$  of the amide nitrogen.

The asymmetric unit is composed of two molecules of interest that are enantiomorphs and one-half of a benzene. A complete set of distances involving the two nitrogens and the proton are found below. It appears that the nitrogens in the fused heterocyclic rings are too far away from the amide proton to be considered a strong hydrogen bond.

Data collection and structure solution were conducted at the X-Ray Crystallographic Laboratory, 160 Kolthoff Hall, Chemistry Department, The University of Minnesota. All calculations were preformed using SGI INDY R4400-SC

or Pentium computers using the SHELXTL V5.0 suite of programs. All publications arising from this report MUST either 1) include Victor G. Young, Jr. as a coauthor or 2) acknowledge both Victor G. Young, Jr. and the X-Ray Crystallographic Laboratory.

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1. SHELXTL-Plus V5.0, Siemens Industrial Automation, Inc., Madison, WI.

Some equations of interest:

$$R_{int} = \sum |F_o|^2 - \langle F_o^2 \rangle | / \sum |F_o|^2 |$$

$$R1 = \sum |||F_o|| - |F_c||| / \sum |F_o|$$

$$wR2 = [\sum [w(F_o^2 - F_c^2)^2] / \sum [w(F_o^2)^2]]^{1/2},$$

$$\text{where } w = q/\sigma^2 (F^2) + (a*p)^2 + b*p$$

$$GooF = S = [\sum [w(F_o^2 - F_c^2)^2] / (n-p)]^2$$

## SHELXL-93 and CIF Archive Format

This note is intended to accompany submissions to journals for the benefit of editors and referees who may not yet be familiar with the features of the new crystal structure refinement program SHELXTL-Plus and the new International Union of Crystallography CIF archive format.

CIF (S.R. Hall, F.H. Allen and I.D. Brown, Acta Crystallogr., A47 (1991) 655-685) is an extremely flexible format for deposition of crystallographic data and is already the method of choice for the transmission of data to the Cambridge (organic) and Inorganic structural databases. At the end of a structure refinement with SHELXTL-Plus two archive files are produced: \*.cif contains the crystal data, atomic coordinates, bond lengths etc., and \*.fcf contains observed and calculated structure factors, both in CIF format. The .fcf file requires no further processing but the .cif file must be edited by the user to include items such as the crystal color that even the most sophisticated program cannot deduce from the diffraction data; this editing takes the form of replacing a question mark with the appropriate information. With a little practice it is perfectly possible for humans to read CIF files, but SHELX users are encouraged to use the program CIFTAB (supplied with SHELXTL-Plus) to produce more tasteful tables of crystal data, bonds and angles, structure factors etc. for referees.

All refinements with SHELXTL-Plus are performed with F-squared rather than F. This enables ALL data to be used rather than only data with F greater than a specified threshold, with the result that the experimental information is more fully exploited. For weakly scattering crystals this can appreciably improve the precision of the structure determination. However the R-index:

$$wR_2 = \sqrt{ \left( \sum [w(F_o^2 - F_c^2)^2] / \sum [wF_o^4] \right) }$$

that (in the absence of restraints) is minimized during the refinement is for statistical reasons about twice as large as the conventional index R1 (based on F):

$$R_1 = \sum |F_o| - |F_c| / \sum |F_o|$$

and to make it worse an R-index based on ALL data is inevitably larger than one based only on data with F greater than a given threshold. It is rumored that a leading journal (that comes out in both German and English editions) has already

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rejected several papers reporting structures refined with the new program  
because "the R-factor was too high" !

Note that wR<sub>2</sub> should not be confused with 'wR' or 'R<sub>w</sub>' (both usually based on F). Since weighting schemes for F-squared and F refinements are quite different, it may not even be possible to calculate a meaningful R<sub>w</sub> if the structure has been refined against F-squared.

For comparison with other (older) structures it is however very desirable to quote a conventional R-index (i.e. R<sub>1</sub>) calculated with a threshold of  $F^2 > 2\sigma(F^2)$  [that effectively corresponds to  $F > 4\sigma(F)$ ]. R<sub>1</sub> also has the advantage that it is relatively insensitive to manipulation of the weighting scheme.

Some very observant referees have drawn authors' attention to the fact that they had not fixed any coordinates to define the origin in polar space groups. This is because SHELXTL-Plus automatically uses the mathematically superior 'polar axis restraints' proposed by H.D. Flack and D. Schwarzenbach (Acta Crystallogr., A44 (1988) 499-506) that restrains a suitable weighted sum of atomic coordinates to be constant. Similarly the Flack 'racemic twinning parameter' is always estimated by the program where appropriate and reported in the .cif file (but not used in the calculation of Fc<sup>2</sup> unless specified by the user), so that it is unlikely that the user will fail to notice when it is necessary to determine the correct 'absolute structure' (H.D. Flack, Acta Crystallogr., A39 (1983) 876-881).

SHELXL-93 uses scattering factors and absorption coefficients from the new Volume C of International Tables for Crystallography (1992), so there will be small discrepancies with values of mu etc. calculated by programs that still use older values.

SHELXL-93 estimates esds in bond lengths, angles and torsion angles from the full covariance matrix. The contributions of the cell esds are also included rigorously, except that the (usually unknown) correlations between the cell parameters are ignored unless defined by the crystal symmetry (e.g. the error in a cubic cell dimension affects the esd of a bond length but not of an angle). The esds in the equations of least-squares planes and in the distances of atoms from such planes are also calculated from the full matrix,

but the (small) contributions of the cell esds to these esds involve some approximations. Thus there will be discrepancies with esds calculated for checking purposes by programs that do not have access to the full covariance matrix.

References:

G.M. Sheldrick, Acta Crystallogr., A46 (1990) 467-473.

SHELXTL-Plus V5.0, Siemens Industrial Automation, Inc., Madison, WI.

**Crystal Data**

Empirical formula	$C_{15.50}H_{16.50}BrN_2O_2$
Crystal Habit, color	Plate, Colorless
Crystal size	0.50 x 0.40 x 0.12 mm
Crystal system	Monoclinic
Space group	$P2_1/c$
	$a = 11.8158(2) \text{ \AA}$ $\alpha = 90^\circ$
	$b = 20.2329(3) \text{ \AA}$ $\beta = 104.4400(10)^\circ$
	$c = 13.2733(3) \text{ \AA}$ $\gamma = 90^\circ$
Volume	$3072.98(10) \text{ \AA}^3$
Z	8
Formula weight	342.72
Density (calculated)	1.482 $\text{Mg/m}^3$
Absorption coefficient	$2.680 \text{ mm}^{-1}$
F(000)	1396

**Data Collection**

Diffraclometer	Siemens SMART Platform CCD
Wavelength	0.71073 $\text{\AA}$
Temperature	173 (2) $K$
$\theta$ range for data collection	1.78 to 24.96 $^\circ$
Index ranges	-13 $\leq$ h $\leq$ 13, -22 $\leq$ k $\leq$ 23, -11 $\leq$ l $\leq$ 15
Reflections collected	14322
Independent reflections	5256 ( $R_{\text{int}} = 0.0824$ )

**Solution and Refinement**

System used	SHELXTL-V5.0
Solution	Direct methods
Refinement method	Full-matrix least-squares on $F^2$
Weighting scheme	$w = [\sigma^2(F_O^2) + (AP)^2 + (BP)]^{-1}$ , where P = $(F_O^2 + 2Fc^2)/3$ , A = 0.0562, and B = 0.0
Absorption correction	SADABS (Sheldrick, 1996)
Max. and min. transmission	0.723 and 0.259
Data / restraints / parameters	5256 / 0 / 407
Final R indices [I>2σ(I)]	$R_1 = 0.0558$ , $wR_2 = 0.1162$
R indices (all data)	$R_1 = 0.1072$ , $wR_2 = 0.1313$
Goodness-of-fit on $F^2$	0.926
Largest diff. peak and hole	0.914 and -0.667 $e\text{\AA}^{-3}$

Table 2. Atomic coordinates [ $x \times 10^4$ ] and equivalent isotropic displacement parameters [ $\text{\AA}^2 \times 10^3$ ] for 96154. U(eq) is defined as one third of the trace of the orthogonalized  $U_{ij}$  tensor.

	x	y	z	U(eq)	SOF
C(1A)	3023 (4)	2533 (2)	4333 (4)	28 (1)	1
C(2A)	2224 (4)	3138 (3)	4286 (5)	39 (2)	1
C(3A)	2791 (4)	3501 (3)	5298 (5)	45 (2)	1
C(4A)	4129 (4)	3415 (3)	5479 (5)	37 (1)	1
N(5A)	4197 (3)	2810 (2)	4826 (3)	32 (1)	1
C(6A)	5036 (5)	2689 (3)	4327 (4)	37 (1)	1
O(6A)	6015 (3)	2963 (2)	4546 (3)	47 (1)	1
C(7A)	4546 (5)	2189 (3)	3483 (5)	42 (2)	1
C(8A)	3201 (5)	2247 (3)	3257 (5)	42 (2)	1
C(9A)	2637 (4)	1966 (2)	4970 (4)	28 (1)	1
O(9A)	1638 (3)	1743 (2)	4667 (3)	42 (1)	1
N(10A)	3453 (3)	1744 (2)	5830 (3)	27 (1)	1
C(11A)	3316 (4)	1238 (2)	6537 (4)	25 (1)	1
C(12A)	2291 (4)	881 (2)	6462 (4)	30 (1)	1
C(13A)	2227 (4)	396 (2)	7199 (4)	33 (1)	1
C(14A)	3209 (4)	273 (2)	8024 (4)	28 (1)	1
C(15A)	4242 (4)	620 (2)	8114 (4)	31 (1)	1
C(16A)	4296 (4)	1106 (2)	7370 (4)	26 (1)	1
Br(1A)	3103 (1)	-389 (1)	9044 (1)	45 (1)	1
C(1B)	999 (4)	7397 (3)	8348 (4)	31 (1)	1
C(2B)	321 (5)	6751 (3)	8293 (5)	49 (2)	1
C(3B)	967 (5)	6400 (3)	9252 (5)	53 (2)	1
C(4B)	2263 (5)	6560 (3)	9400 (5)	43 (2)	1
N(5B)	2219 (4)	7181 (2)	8758 (4)	38 (1)	1
C(6B)	2981 (5)	7350 (3)	8220 (5)	44 (2)	1
O(6B)	4004 (3)	7127 (2)	8385 (3)	53 (1)	1
C(7B)	2378 (5)	7844 (3)	7410 (5)	42 (2)	1
C(8B)	1054 (5)	7745 (3)	7273 (4)	45 (2)	1
C(9B)	571 (4)	7909 (2)	9046 (4)	27 (1)	1
O(9B)	-468 (3)	8026 (2)	8887 (3)	45 (1)	1
N(10B)	1437 (3)	8210 (2)	9805 (3)	25 (1)	1
C(11B)	1289 (4)	8722 (2)	10496 (4)	23 (1)	1
C(12B)	217 (4)	9056 (2)	10405 (4)	27 (1)	1
C(13B)	144 (4)	9570 (2)	11098 (4)	28 (1)	1
C(14B)	1111 (4)	9757 (2)	11884 (4)	27 (1)	1
C(15B)	2183 (4)	9422 (2)	11990 (4)	30 (1)	1
C(16B)	2257 (4)	8910 (2)	11303 (4)	26 (1)	1
Br(1B)	990 (1)	10470 (1)	12801 (1)	42 (1)	1
C(1C)	4448 (7)	9721 (4)	15725 (7)	71 (2)	1
C(2C)	3799 (7)	10076 (4)	14850 (6)	66 (2)	1
C(3C)	4360 (7)	10352 (4)	14139 (6)	66 (2)	1

Table 3. Bond lengths [Å] and angles [°] for 3d.

C(1A)-N(5A)	1.487(6)	C(1A)-C(2A)	1.538(7)
C(1A)-C(9A)	1.561(7)	C(1A)-C(8A)	1.602(7)
C(2A)-C(3A)	1.531(7)	C(2A)-H(2AA)	0.97
C(2A)-H(2AB)	0.97	C(3A)-C(4A)	1.548(7)
C(3A)-H(3AA)	0.97	C(3A)-H(3AB)	0.97
C(4A)-N(5A)	1.514(6)	C(4A)-H(4AA)	0.97
C(4A)-H(4AB)	0.97	N(5A)-C(6A)	1.344(6)
C(6A)-O(6A)	1.250(6)	C(6A)-C(7A)	1.513(7)
C(7A)-C(8A)	1.547(7)	C(7A)-H(7AA)	0.97
C(7A)-H(7AB)	0.97	C(8A)-H(8AA)	0.97
C(8A)-H(8AB)	0.97	C(9A)-O(9A)	1.233(5)
C(9A)-N(10A)	1.374(6)	N(10A)-C(11A)	1.424(6)
N(10A)-H(10A)	0.74(5)	N(5A)-H(10A)	2.35(5)
N(5A)-N(10A)	2.790(6)	C(11A)-C(12A)	1.393(6)
C(11A)-C(16A)	1.413(7)	C(12A)-C(13A)	1.402(7)
C(12A)-H(12A)	0.93	C(13A)-C(14A)	1.404(7)
C(13A)-H(13A)	0.93	C(14A)-C(15A)	1.387(6)
C(14A)-Br(1A)	1.931(5)	C(15A)-C(16A)	1.406(7)
C(15A)-H(15A)	0.93	C(16A)-H(16A)	0.93
C(1B)-N(5B)	1.475(6)	C(1B)-C(2B)	1.525(7)
C(1B)-C(9B)	1.556(7)	C(1B)-C(8B)	1.607(7)
C(2B)-C(3B)	1.490(8)	C(2B)-H(2BA)	0.97
C(2B)-H(2BB)	0.97	C(3B)-C(4B)	1.529(7)
C(3B)-H(3BA)	0.97	C(3B)-H(3BB)	0.97
C(4B)-N(5B)	1.512(7)	C(4B)-H(4BA)	0.97
C(4B)-H(4BB)	0.97	N(5B)-C(6B)	1.326(7)
C(6B)-O(6B)	1.258(6)	C(6B)-C(7B)	1.510(8)
C(7B)-C(8B)	1.543(7)	C(7B)-H(7BA)	0.97
C(7B)-H(7BB)	0.97	C(8B)-H(8BA)	0.97
C(8B)-H(8BB)	0.97	C(9B)-O(9B)	1.216(5)
C(9B)-N(10B)	1.385(6)	N(10B)-C(11B)	1.423(6)
N(10B)-H(10B)	0.81(4)	N(5B)-H(10B)	2.37(5)
N(5B)-N(10B)	2.785(6)	C(11B)-C(16B)	1.411(7)
C(11B)-C(12B)	1.414(6)	C(12B)-C(13B)	1.405(7)
C(12B)-H(12B)	0.93	C(13B)-C(14B)	1.394(7)
C(13B)-H(13B)	0.93	C(14B)-C(15B)	1.413(6)
C(14B)-Br(1B)	1.916(5)	C(15B)-C(16B)	1.397(6)
C(15B)-H(15B)	0.93	C(16B)-H(16B)	0.93
C(1C)-C(3C) #1	1.383(9)	C(1C)-C(2C)	1.417(10)
C(1C)-H(1CA)	0.93	C(2C)-C(3C)	1.398(10)
C(2C)-H(2CA)	0.93	C(3C)-C(1C) #1	1.383(9)
C(3C)-H(3CA)	0.93		
N(5A)-C(1A)-C(2A)	102.4(4)	N(5A)-C(1A)-C(9A)	113.9(4)
C(2A)-C(1A)-C(9A)	110.3(4)	N(5A)-C(1A)-C(8A)	102.3(4)
C(2A)-C(1A)-C(8A)	117.9(5)	C(9A)-C(1A)-C(8A)	109.8(4)
C(3A)-C(2A)-C(1A)	102.5(4)	C(3A)-C(2A)-H(2AA)	111.3(3)
C(1A)-C(2A)-H(2AA)	111.3(3)	C(3A)-C(2A)-H(2AB)	111.3(3)
C(1A)-C(2A)-H(2AB)	111.3(3)	H(2AA)-C(2A)-H(2AB)	109.2
C(2A)-C(3A)-C(4A)	106.8(5)	C(2A)-C(3A)-H(3AA)	110.4(3)
C(4A)-C(3A)-H(3AA)	110.4(3)	C(2A)-C(3A)-H(3AB)	110.4(3)
C(4A)-C(3A)-H(3AB)	110.4(3)	H(3AA)-C(3A)-H(3AB)	108.6
N(5A)-C(4A)-C(3A)	101.5(4)	N(5A)-C(4A)-H(4AA)	111.5(3)
C(3A)-C(4A)-H(4AA)	111.5(3)	N(5A)-C(4A)-H(4AB)	111.5(3)
C(3A)-C(4A)-H(4AB)	111.5(3)	H(4AA)-C(4A)-H(4AB)	109.3
C(6A)-N(5A)-C(1A)	115.9(5)	C(6A)-N(5A)-C(4A)	125.4(4)
C(1A)-N(5A)-C(4A)	112.3(4)	O(6A)-C(6A)-N(5A)	123.9(5)
O(6A)-C(6A)-C(7A)	129.0(5)	N(5A)-C(6A)-C(7A)	107.0(5)
C(6A)-C(7A)-C(8A)	106.1(4)	C(6A)-C(7A)-H(7AA)	110.5(3)

C(8A)-C(7A)-H(7AA)	110.5(3)	C(6A)-C(7A)-H(7AB)	110.5(3)
C(8A)-C(7A)-H(7AB)	110.5(3)	H(7AA)-C(7A)-H(7AB)	108.7
C(7A)-C(8A)-C(1A)	102.2(4)	C(7A)-C(8A)-H(8AA)	111.3(3)
C(1A)-C(8A)-H(8AA)	111.3(3)	C(7A)-C(8A)-H(8AB)	111.3(3)
C(1A)-C(8A)-H(8AB)	111.3(3)	H(8AA)-C(8A)-H(8AB)	109.2
O(9A)-C(9A)-N(10A)	124.7(5)	O(9A)-C(9A)-C(1A)	118.5(4)
N(10A)-C(9A)-C(1A)	116.8(4)	C(9A)-N(10A)-C(11A)	127.6(4)
C(9A)-N(10A)-H(10A)	111(4)	C(11A)-N(10A)-H(10A)	121(4)
C(12A)-C(11A)-C(16A)	119.0(5)	C(12A)-C(11A)-N(10A)	124.4(4)
C(16A)-C(11A)-N(10A)	116.5(4)	C(11A)-C(12A)-C(13A)	120.7(5)
C(11A)-C(12A)-H(12A)	119.6(3)	C(13A)-C(12A)-H(12A)	119.6(3)
C(12A)-C(13A)-C(14A)	119.3(5)	C(12A)-C(13A)-H(13A)	120.3(3)
C(14A)-C(13A)-H(13A)	120.3(3)	C(15A)-C(14A)-C(13A)	121.1(5)
C(15A)-C(14A)-Br(1A)	120.0(4)	C(13A)-C(14A)-Br(1A)	118.9(4)
C(14A)-C(15A)-C(16A)	119.1(5)	C(14A)-C(15A)-H(15A)	120.5(3)
C(16A)-C(15A)-H(15A)	120.5(3)	C(15A)-C(16A)-C(11A)	120.8(5)
C(15A)-C(16A)-H(16A)	119.6(3)	C(11A)-C(16A)-H(16A)	119.6(3)
N(5B)-C(1B)-C(2B)	102.5(4)	N(5B)-C(1B)-C(9B)	114.2(4)
C(2B)-C(1B)-C(9B)	110.7(4)	N(5B)-C(1B)-C(8B)	101.9(4)
C(2B)-C(1B)-C(8B)	118.1(5)	C(9B)-C(1B)-C(8B)	109.2(4)
C(3B)-C(2B)-C(1B)	102.5(5)	C(3B)-C(2B)-H(2BA)	111.3(3)
C(1B)-C(2B)-H(2BA)	111.3(3)	C(3B)-C(2B)-H(2BB)	111.3(4)
C(1B)-C(2B)-H(2BB)	111.3(3)	H(2BA)-C(2B)-H(2BB)	109.2
C(2B)-C(3B)-C(4B)	107.0(5)	C(2B)-C(3B)-H(3BA)	110.3(3)
C(4B)-C(3B)-H(3BA)	110.3(3)	C(2B)-C(3B)-H(3BB)	110.3(4)
C(4B)-C(3B)-H(3BB)	110.3(3)	H(3BA)-C(3B)-H(3BB)	108.6
N(5B)-C(4B)-C(3B)	102.1(4)	N(5B)-C(4B)-H(4BA)	111.3(3)
C(3B)-C(4B)-H(4BA)	111.3(3)	N(5B)-C(4B)-H(4BB)	111.3(3)
C(3B)-C(4B)-H(4BB)	111.3(3)	H(4BA)-C(4B)-H(4BB)	109.2
C(6B)-N(5B)-C(1B)	117.2(5)	C(6B)-N(5B)-C(4B)	125.8(5)
C(1B)-N(5B)-C(4B)	110.4(4)	O(6B)-C(6B)-N(5B)	124.4(6)
O(6B)-C(6B)-C(7B)	128.6(6)	N(5B)-C(6B)-C(7B)	107.0(5)
C(6B)-C(7B)-C(8B)	106.4(5)	C(6B)-C(7B)-H(7BA)	110.5(3)
C(8B)-C(7B)-H(7BA)	110.5(3)	C(6B)-C(7B)-H(7BB)	110.5(3)
C(8B)-C(7B)-H(7BB)	110.5(3)	H(7BA)-C(7B)-H(7BB)	108.6
C(7B)-C(8B)-C(1B)	102.5(4)	C(7B)-C(8B)-H(8BA)	111.3(3)
C(1B)-C(8B)-H(8BA)	111.3(3)	C(7B)-C(8B)-H(8BB)	111.3(3)
C(1B)-C(8B)-H(8BB)	111.3(3)	H(8BA)-C(8B)-H(8BB)	109.2
O(9B)-C(9B)-N(10B)	124.8(5)	O(9B)-C(9B)-C(1B)	119.4(4)
N(10B)-C(9B)-C(1B)	115.8(4)	C(9B)-N(10B)-C(11B)	127.0(4)
C(9B)-N(10B)-H(10B)	118(4)	C(11B)-N(10B)-H(10B)	116(4)
C(16B)-C(11B)-C(12B)	118.4(5)	C(16B)-C(11B)-N(10B)	118.6(4)
C(12B)-C(11B)-N(10B)	123.0(4)	C(13B)-C(12B)-C(11B)	119.9(5)
C(13B)-C(12B)-H(12B)	120.1(3)	C(11B)-C(12B)-H(12B)	120.1(3)
C(14B)-C(13B)-C(12B)	121.2(4)	C(14B)-C(13B)-H(13B)	119.4(3)
C(12B)-C(13B)-H(13B)	119.4(3)	C(13B)-C(14B)-C(15B)	119.4(5)
C(13B)-C(14B)-Br(1B)	120.2(4)	C(15B)-C(14B)-Br(1B)	120.3(4)
C(16B)-C(15B)-C(14B)	119.4(5)	C(16B)-C(15B)-H(15B)	120.3(3)
C(14B)-C(15B)-H(15B)	120.3(3)	C(15B)-C(16B)-C(11B)	121.6(4)
C(15B)-C(16B)-H(16B)	119.2(3)	C(11B)-C(16B)-H(16B)	119.2(3)
C(3C) #1-C(1C)-C(2C)	119.1(8)	C(3C) #1-C(1C)-H(1CA)	120.5(6)
C(2C)-C(1C)-H(1CA)	120.5(5)	C(3C)-C(2C)-C(1C)	120.4(7)
C(3C)-C(2C)-H(2CA)	119.8(5)	C(1C)-C(2C)-H(2CA)	119.8(5)
C(1C) #1-C(3C)-C(2C)	120.6(8)	C(1C) #1-C(3C)-H(3CA)	119.7(6)
C(2C)-C(3C)-H(3CA)	119.7(4)		

Symmetry transformations used to generate equivalent atoms:

#1 -x+1, -y+2, -z+3

Table 4. Anisotropic displacement parameters [ $\text{\AA}^2 \times 10^3$ ] for 96154. The anisotropic displacement factor exponent takes the form:  $-2\pi [ (ha)^2 U_{11} + \dots + 2hka b U_{12} ]$

	U11	U22	U33	U23	U13	U12
C(1A)	14(3)	36(3)	33(3)	8(3)	4(2)	-5(2)
C(2A)	22(3)	50(4)	44(4)	12(3)	4(3)	-4(3)
C(3A)	34(4)	51(4)	53(5)	0(3)	12(3)	-6(3)
C(4A)	30(3)	44(4)	33(4)	1(3)	5(3)	-6(3)
N(5A)	14(2)	48(3)	32(3)	8(2)	2(2)	-3(2)
C(6A)	35(3)	41(4)	34(4)	17(3)	8(3)	6(3)
O(6A)	16(2)	72(3)	51(3)	26(2)	2(2)	-9(2)
C(7A)	40(4)	51(4)	41(4)	-1(3)	20(3)	-5(3)
C(8A)	40(4)	49(4)	38(4)	1(3)	12(3)	-6(3)
C(9A)	19(3)	37(3)	28(3)	-2(3)	4(2)	-3(2)
O(9A)	24(2)	56(2)	40(3)	16(2)	-5(2)	-13(2)
N(10A)	13(2)	42(3)	23(3)	5(2)	0(2)	-6(2)
C(11A)	20(3)	32(3)	26(3)	1(2)	10(2)	-3(2)
C(12A)	17(3)	34(3)	33(3)	4(3)	-1(3)	-4(2)
C(13A)	25(3)	33(3)	44(4)	3(3)	14(3)	-3(3)
C(14A)	29(3)	30(3)	28(3)	13(2)	13(2)	3(2)
C(15A)	26(3)	34(3)	30(3)	2(3)	2(3)	2(2)
C(16A)	19(3)	32(3)	27(3)	-1(3)	6(2)	-6(2)
Br(1A)	40(1)	47(1)	48(1)	21(1)	10(1)	1(1)
C(1B)	14(3)	42(3)	37(4)	-7(3)	4(2)	5(2)
C(2B)	37(4)	53(4)	56(5)	-11(4)	12(3)	-4(3)
C(3B)	55(4)	49(4)	56(5)	-5(4)	15(4)	-1(3)
C(4B)	49(4)	42(4)	37(4)	-3(3)	8(3)	13(3)
N(5B)	23(3)	55(3)	33(3)	-9(2)	4(2)	1(2)
C(6B)	33(4)	63(4)	35(4)	-18(3)	4(3)	-5(3)
O(6B)	21(2)	88(3)	45(3)	-30(2)	0(2)	9(2)
C(7B)	40(4)	45(4)	43(4)	-6(3)	17(3)	0(3)
C(8B)	44(4)	65(4)	25(4)	0(3)	6(3)	15(3)
C(9B)	27(3)	31(3)	23(3)	0(2)	6(2)	-2(2)
O(9B)	18(2)	65(3)	52(3)	-18(2)	7(2)	4(2)
N(10B)	16(2)	32(3)	26(3)	-1(2)	5(2)	2(2)
C(11B)	23(3)	23(3)	25(3)	2(2)	9(2)	2(2)
C(12B)	21(3)	33(3)	28(3)	5(3)	7(3)	1(2)
C(13B)	20(3)	32(3)	36(3)	9(3)	12(2)	12(2)
C(14B)	37(3)	20(3)	28(3)	0(2)	14(3)	-3(2)
C(15B)	22(3)	32(3)	34(3)	0(3)	5(3)	1(2)
C(16B)	18(3)	33(3)	27(3)	-1(2)	7(2)	3(2)
Br(1B)	42(1)	38(1)	45(1)	-12(1)	10(1)	4(1)
C(1C)	64(5)	77(5)	68(6)	-31(5)	9(5)	-15(4)
C(2C)	45(5)	74(5)	68(6)	-35(5)	-7(4)	7(4)
C(3C)	60(5)	68(5)	56(5)	-31(4)	-11(4)	5(4)

Table 5. Torsion angles [°] for 3d .

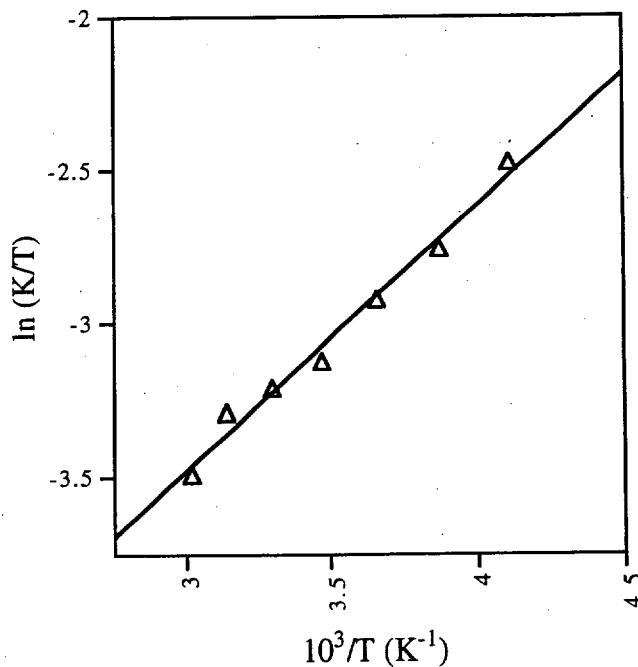
N(5A)-C(1A)-C(2A)-C(3A)	-36.2(5)	C(9A)-C(1A)-C(2A)-C(3A)	85.4(5)
C(8A)-C(1A)-C(2A)-C(3A)	-147.5(5)	C(1A)-C(2A)-C(3A)-C(4A)	36.5(6)
C(2A)-C(3A)-C(4A)-N(5A)	-21.3(6)	C(2A)-C(1A)-N(5A)-C(6A)	-128.9(5)
C(9A)-C(1A)-N(5A)-C(6A)	112.0(5)	C(8A)-C(1A)-N(5A)-C(6A)	-6.4(6)
C(2A)-C(1A)-N(5A)-C(4A)	24.6(5)	C(9A)-C(1A)-N(5A)-C(4A)	-94.5(5)
C(8A)-C(1A)-N(5A)-C(4A)	147.1(4)	C(3A)-C(4A)-N(5A)-C(6A)	148.0(5)
C(3A)-C(4A)-N(5A)-C(1A)	-2.4(6)	C(1A)-N(5A)-C(6A)-O(6A)	169.1(5)
C(4A)-N(5A)-C(6A)-O(6A)	19.5(8)	C(1A)-N(5A)-C(6A)-C(7A)	-10.0(6)
C(4A)-N(5A)-C(6A)-C(7A)	-159.5(5)	O(6A)-C(6A)-C(7A)-C(8A)	-156.3(5)
N(5A)-C(6A)-C(7A)-C(8A)	22.7(6)	C(6A)-C(7A)-C(8A)-C(1A)	-25.3(6)
N(5A)-C(1A)-C(8A)-C(7A)	19.2(5)	C(2A)-C(1A)-C(8A)-C(7A)	130.5(5)
C(9A)-C(1A)-C(8A)-C(7A)	-102.1(5)	N(5A)-C(1A)-C(9A)-O(9A)	174.1(4)
C(2A)-C(1A)-C(9A)-O(9A)	59.6(6)	C(8A)-C(1A)-C(9A)-O(9A)	-72.0(6)
N(5A)-C(1A)-C(9A)-N(10A)	-6.7(6)	C(2A)-C(1A)-C(9A)-N(10A)	-121.2(5)
C(8A)-C(1A)-C(9A)-N(10A)	107.3(5)	O(9A)-C(9A)-N(10A)-C(11A)	-1.2(8)
C(1A)-C(9A)-N(10A)-C(11A)	179.6(4)	C(9A)-N(10A)-C(11A)-C(12A)	-0.4(8)
C(9A)-N(10A)-C(11A)-C(16A)	-179.6(5)	C(16A)-C(11A)-C(12A)-C(13A)	-0.1(7)
N(10A)-C(11A)-C(12A)-C(13A)	-179.2(5)	C(11A)-C(12A)-C(13A)-C(14A)	0.3(8)
C(12A)-C(13A)-C(14A)-C(15A)	-0.5(8)	C(12A)-C(13A)-C(14A)-Br(1A)	179.2(4)
C(13A)-C(14A)-C(15A)-C(16A)	0.6(8)	Br(1A)-C(14A)-C(15A)-C(16A)	-179.2(4)
C(14A)-C(15A)-C(16A)-C(11A)	-0.3(7)	C(12A)-C(11A)-C(16A)-C(15A)	0.1(7)
N(10A)-C(11A)-C(16A)-C(15A)	179.3(4)	N(5B)-C(1B)-C(2B)-C(3B)	38.2(6)
C(9B)-C(1B)-C(2B)-C(3B)	-84.0(5)	C(8B)-C(1B)-C(2B)-C(3B)	149.1(5)
C(1B)-C(2B)-C(3B)-C(4B)	-36.8(6)	C(2B)-C(3B)-C(4B)-N(5B)	20.3(6)
C(2B)-C(1B)-N(5B)-C(6B)	126.4(5)	C(9B)-C(1B)-N(5B)-C(6B)	-113.8(5)
C(8B)-C(1B)-N(5B)-C(6B)	3.8(6)	C(2B)-C(1B)-N(5B)-C(4B)	-26.7(6)
C(9B)-C(1B)-N(5B)-C(4B)	93.1(5)	C(8B)-C(1B)-N(5B)-C(4B)	-149.3(4)
C(3B)-C(4B)-N(5B)-C(6B)	-145.7(5)	C(3B)-C(4B)-N(5B)-C(1B)	4.6(6)
C(1B)-N(5B)-C(6B)-O(6B)	-169.4(5)	C(4B)-N(5B)-C(6B)-O(6B)	-21.0(9)
C(1B)-N(5B)-C(6B)-C(7B)	10.6(7)	C(4B)-N(5B)-C(6B)-C(7B)	159.1(5)
O(6B)-C(6B)-C(7B)-C(8B)	159.1(6)	N(5B)-C(6B)-C(7B)-C(8B)	-20.9(6)
C(6B)-C(7B)-C(8B)-C(1B)	22.2(6)	N(5B)-C(1B)-C(8B)-C(7B)	-15.8(5)
C(2B)-C(1B)-C(8B)-C(7B)	-127.2(5)	C(9B)-C(1B)-C(8B)-C(7B)	105.3(5)
N(5B)-C(1B)-C(9B)-O(9B)	-166.4(5)	C(2B)-C(1B)-C(9B)-O(9B)	-51.3(6)
C(8B)-C(1B)-C(9B)-O(9B)	80.3(6)	N(5B)-C(1B)-C(9B)-N(10B)	14.9(6)
C(2B)-C(1B)-C(9B)-N(10B)	130.0(5)	C(8B)-C(1B)-C(9B)-N(10B)	-98.4(5)
O(9B)-C(9B)-N(10B)-C(11B)	-3.1(8)	C(1B)-C(9B)-N(10B)-C(11B)	175.6(4)
C(9B)-N(10B)-C(11B)-C(16B)	172.2(5)	C(9B)-N(10B)-C(11B)-C(12B)	-8.1(7)
C(16B)-C(11B)-C(12B)-C(13B)	1.4(7)	N(10B)-C(11B)-C(12B)-C(13B)	-178.2(4)
C(11B)-C(12B)-C(13B)-C(14B)	-0.5(7)	C(12B)-C(13B)-C(14B)-C(15B)	-0.3(7)
C(12B)-C(13B)-C(14B)-Br(1B)	178.9(4)	C(13B)-C(14B)-C(15B)-C(16B)	0.2(7)
Br(1B)-C(14B)-C(15B)-C(16B)	-179.0(4)	C(14B)-C(15B)-C(16B)-C(11B)	0.7(7)
C(12B)-C(11B)-C(16B)-C(15B)	-1.5(7)	N(10B)-C(11B)-C(16B)-C(15B)	178.1(4)
C(3C) #1-C(1C)-C(2C)-C(3C)	-0.5(11)	C(1C)-C(2C)-C(3C)-C(1C) #1	0.5(11)

Symmetry transformations used to generate equivalent atoms:

#1 -x+1, -y+2, -z+3

Table 6. Hydrogen coordinates  
displacement parameters ( $\text{\AA}^2 \times 10^3$ ) for 3d

	x	y	z	U(eq)
H(2AA)	2218 (4)	3410 (3)	3683 (5)	66 (20)
H(2AB)	1430 (4)	3006 (3)	4268 (5)	30 (14)
H(3AA)	2529 (4)	3314 (3)	5873 (5)	68 (21)
H(3AB)	2585 (4)	3966 (3)	5239 (5)	56 (19)
H(4AA)	4483 (4)	3797 (3)	5237 (5)	45 (16)
H(4AB)	4503 (4)	3338 (3)	6207 (5)	66 (20)
H(7AA)	4798 (5)	1746 (3)	3718 (5)	64 (20)
H(7AB)	4809 (5)	2285 (3)	2862 (5)	63 (19)
H(8AA)	2828 (5)	1820 (3)	3097 (5)	49 (17)
H(8AB)	2896 (5)	2548 (3)	2686 (5)	69 (21)
H(10A)	4031 (41)	1888 (24)	5851 (41)	32
H(12A)	1642 (4)	965 (2)	5916 (4)	21 (13)
H(13A)	1541 (4)	157 (2)	7143 (4)	45 (16)
H(15A)	4890 (4)	533 (2)	8660 (4)	50 (17)
H(16A)	4983 (4)	1342 (2)	7427 (4)	40 (15)
H(2BA)	-485 (5)	6831 (3)	8304 (5)	34 (15)
H(2BB)	339 (5)	6502 (3)	7673 (5)	88 (25)
H(3BA)	839 (5)	5927 (3)	9175 (5)	58 (19)
H(3BB)	701 (5)	6549 (3)	9848 (5)	67 (21)
H(4BA)	2643 (5)	6639 (3)	10126 (5)	89 (25)
H(4BB)	2666 (5)	6206 (3)	9139 (5)	14 (12)
H(7BA)	2587 (5)	7767 (3)	6757 (5)	46 (17)
H(7BB)	2604 (5)	8291 (3)	7639 (5)	27 (14)
H(8BA)	724 (5)	7463 (3)	6682 (4)	127 (32)
H(8BB)	643 (5)	8165 (3)	7183 (4)	62 (20)
H(10B)	2104 (40)	8086 (23)	9867 (38)	30
H(12B)	-439 (4)	8935 (2)	9889 (4)	66 (20)
H(13B)	-563 (4)	9790 (2)	11030 (4)	19 (12)
H(15B)	2834 (4)	9541 (2)	12513 (4)	28 (13)
H(16B)	2962 (4)	8687 (2)	11381 (4)	20 (13)
H(1CA)	4077 (7)	9540 (4)	16202 (7)	87 (28)
H(2CA)	2996 (7)	10125 (4)	14748 (6)	104 (28)
H(3CA)	3928 (7)	10587 (4)	13570 (6)	100 (29)



**Supporting Figure S3.** *Van't Hoff plot of the cis-trans ratio of proline **1k***

**Procedure A. General Synthesis of Prolines **1** and **2**.** To approximately 500 mg of N-substituted proline (1 equiv) and 1 equiv amine or alcohol (and a catalytic amount of 4-pyrrolidinopyridine for ester synthesis) stirring at 0 °C in approximately 20 mL CH<sub>2</sub>Cl<sub>2</sub> was added 1.1 equiv EDCI in one portion. The reaction was allowed to stir 2 h at 0 °C and then at rt until judged complete by TLC. The reaction mixture was diluted with 50 mL CH<sub>2</sub>Cl<sub>2</sub> and washed with 5% citric acid (3 x 50 mL) and then with saturated NaHCO<sub>3</sub> (2 x 50 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and then concentrated by rotary evaporation. The crude material was purified by either recrystallization or by flash column chromatography.

**1-(2-Fluorobenzoyl)-N-hexyl-2-pyrrolidinecarboxamide (**1a**).** Proline **15** and hexylamine were coupled by Procedure A and chromatography with 25-50% EtOAc/hexanes yielded 63% of **1a** as a colorless oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.5-7.4 (m, 2 H), 7.2 (m, 1 H), 7.1 (m, 1 H), 7.0 (s, 0.9 H), 6.1 (s, 0.1 H), 4.8 (dd, 0.9 H), 4.2 (dd, 0.1 H), 3.9-3.7 (m, 0.2 H), 3.5 (m, 1 H), 3.4-3.2 (m, 2.6 H), 3.0 (m, 0.2 H), 2.5 (m, 1 H), 2.1-1.8

(m, 3 H), 1.5 (m, 2 H), 1.4-1.2 (m, 6 H), 0.9 (m, 3 H) ppm;  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  170.4, 166.5, 159.4, 156.9, 131.7, 131.6, 128.5, 128.4, 124.7, 124.64, 124.61, 124.55, 116.0, 115.7, 59.8, 48.7, 48.6, 39.5, 31.4, 29.3, 27.6, 26.4, 24.7, 22.5, 13.9 ppm;  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -115.6 (m, 0.1 F), -116.1 (m, 0.9 F) ppm; IR (neat) 3307, 1658, 1634  $\text{cm}^{-1}$ ; HRMS (EI) calcd mass 320.1900. Found: 320.1901. Anal. Calcd for  $\text{C}_{18}\text{H}_{25}\text{FN}_2\text{O}_2$ : C, 67.48; H, 7.86; N, 8.74. Found: C, 67.40; H, 7.82; N, 8.64.

**1-Acetyl-N-(4-methoxyphenyl)-2-pyrrolidinecarboxamide (1c).** N-Acetylproline and 4-anisidine were coupled by Procedure A and chromatography with 50-75% EtOAc/hexanes followed by recrystallization from  $\text{CH}_2\text{Cl}_2$ /pentane yielded 54% of **1c** as a pale brown solid.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.5 (s, 0.95 H), 8.1 (s, 0.05 H), 7.4 (d, 2 H), 6.8 (d, 2 H), 4.7 (dd, 0.95 H), 4.4 (dd, 0.05 H), 3.8 (s, 0.15 H), 3.77 (s, 2.85 H), 3.6 (m, 1 H), 3.4 (m, 1 H), 2.5 (m, 1 H), 2.1 (s, 2.85 H), 2.1-1.9 (m, 2 H), 2.0 (s, 0.15 H), 1.8 (m, 1 H) ppm;  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  171.5, 168.5, 155.9, 131.5, 121.1, 121.0, 114.1, 113.9, 60.3, 55.5, 55.4, 48.5, 48.4, 26.9, 26.8, 25.1, 25.0, 22.5 ppm; IR (KBr) 3340, 1671, 1618  $\text{cm}^{-1}$ ; HRMS (EI) calcd mass 262.1317. Found: 262.1319. Anal. Calcd for  $\text{C}_{14}\text{H}_{18}\text{N}_2\text{O}_3$ : C, 64.11; H, 6.92; N, 10.68. Found: C, 64.14; H, 6.94; N, 10.61.

**1-Acetyl-N-(4-(dimethylamino)phenyl)-2-pyrrolidinecarboxamide (1d).** N-Acetylproline and N,N-dimethyl-1,4-phenylenediamine dihydrochloride were coupled by Procedure A with slight modifications: 1) To soak up the HCl present, 2 equiv of triethylamine was added to the mixture; 2) the reaction was carried out in the dark; and 3) the reaction could not be worked up with acid, so the wash was limited to saturated  $\text{NaHCO}_3$ . Chromatography with 50-100% EtOAc/hexanes yielded 40% of **1d** as a pale yellow solid.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.4 (s, 0.9 H), 8.0 (s, 0.1 H), 7.4 (d, 2 H), 6.6 (d, 2 H), 4.7 (d, 0.9 H), 4.3 (dd, 0.1 H), 3.6 (m, 1 H), 3.4 (m, 1 H), 2.92 (s, 0.6), 2.90 (s, 5.4 H), 2.5 (m, 1 H), 2.2-2.1 (m, 1 H), 2.1 (s, 2.7 H), 2.05 (s, 0.3 H), 2.0 (m, 1 H), 1.8 (m, 1 H) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  171.3, 168.3, 147.6, 128.4, 122.0, 121.0, 113.0, 112.7, 62.6, 60.1, 48.3, 46.8, 40.9, 40.7, 32.1, 26.8, 24.9, 22.4 ppm; IR ( $\text{CH}_2\text{Cl}_2$ ) 3290, 1684, 1620  $\text{cm}^{-1}$ ; Anal. Calcd for  $\text{C}_{15}\text{H}_{21}\text{N}_3\text{O}_2$ : C, 65.43; H, 7.69; N, 15.26. Found: C, 65.42; H, 7.63; N, 15.15.

**4-[(1-Acetyl-2-pyrrolidinyl)carbonyl]amino]-benzoic acid methyl ester (1e).** To 500 mg of N-acetylproline (3.2 mmol) stirring at rt in approximately 20 mL  $\text{CH}_2\text{Cl}_2$  was added 310  $\mu\text{L}$  oxalyl chloride (3.5 mmol) followed by 1 drop of DMF. The mixture was allowed to stir for 1 h, and was then cooled to -78 °C. Addition of 480 mg methyl 4-amino benzoate (3.2 mmol) was followed by 0.90 mL triethylamine (6.4 mmol),

and the reaction was allowed to warm and stir at rt 2 h. The reaction mixture was diluted with 50 mL CH<sub>2</sub>Cl<sub>2</sub> and washed with 1.0 M HCl (3 x 50 mL) and then with saturated NaHCO<sub>3</sub> (2 x 50 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and then concentrated by rotary evaporation. The crude material was recrystallized from CH<sub>2</sub>Cl<sub>2</sub>/pentane to yield 671 mg (73%) of **1e** as a fluffy white solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 10.0 (s, 1 H), 8.0 (d, 2 H), 7.6 (d, 2 H), 4.8 (d, 1 H), 3.9 (s, 3 H), 3.6 (m, 1 H), 3.5 (m, 1 H), 2.6 (m, 1 H), 2.2 (s, 3 H), 2.2-2.0 (m, 2 H), 1.9 (m, 1 H) ppm; <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 172.2, 169.0, 166.7, 142.5, 130.7, 125.2, 118.9, 60.6, 51.9, 48.6, 26.2, 25.1, 22.6 ppm; IR (CH<sub>2</sub>Cl<sub>2</sub>) 3271, 1750, 1708, 1630 cm<sup>-1</sup>; HRMS (EI) calcd mass 290.1267. Found: 290.1267. Anal. Calcd for C<sub>15</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub>: C, 62.06; H, 6.25; N, 9.65. Found: C, 61.95; H, 6.24; N, 9.58.

**1-Acetyl-N-(phenylmethyl)-2-pyrrolidinecarboxamide (1f).** N-Acetylproline and benzyl amine were coupled by Procedure A and without additional purification yielded 80% of **1f** as an analytically pure white solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.5 (s, 0.85 H), 7.4-7.2 (m, 5 H), 6.6 (s, 0.15 H), 4.6 (dd, 0.85 H), 4.5 (dd, 1.15 H), 4.4-4.3 (dd, 1 H), 3.6 (m, 1 H), 3.4 (m, 1 H), 2.5 (m, 1 H), 2.2-2.1 (m, 1 H), 2.1 (s, 2.55 H), 2.0 (m, 1 H), 1.95 (s, 0.45 H), 1.9-1.8 (m, 1 H) ppm; <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 171.1, 171.0, 138.3, 128.8, 128.5, 127.7, 127.6, 127.4, 127.1, 62.4, 59.6, 48.3, 46.7, 43.5, 43.3, 43.2, 32.0, 27.3, 25.0, 22.9, 22.5 ppm; IR (CH<sub>2</sub>Cl<sub>2</sub>) 3295, 1676, 1627 cm<sup>-1</sup>; Anal. Calcd for C<sub>14</sub>H<sub>18</sub>N<sub>2</sub>O<sub>2</sub>: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.28; H, 7.39; N, 11.31.

**2-[[[(2-Fluorophenyl)methyl]amino]carbonyl]-1-pyrrolidinecarboxylic acid phenylmethyl ester (1g).** CBZ-Proline and 2-fluorobenzylamine were coupled by Procedure A and recrystallization from CH<sub>2</sub>Cl<sub>2</sub>/hexane yielded 69% of **1g** as a fluffy white solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 0 °C) δ 7.5-7.0 (m, 9.6 H), 6.5 (s, 0.4 H), 5.2-5.0 (m, 2 H), 4.6-4.3 (m, 3 H), 3.6-3.4 (m, 2 H), 2.4 (m, 1 H), 2.2 (m, 1 H), 2.0-1.8 (m, 2 H) ppm; <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>, 0 °C) δ 171.6, 161.6, 159.7, 156.2, 155.1, 136.1, 135.9, 129.8, 129.5, 129.3, 129.2, 129.0, 128.9, 128.5, 128.1, 127.8, 124.2, 115.4, 115.3, 115.2, 115.1, 67.3, 61.0, 60.5, 47.5, 47.0, 37.3, 31.0, 28.3, 24.5, 23.6 ppm; <sup>19</sup>F NMR (470 MHz, CDCl<sub>3</sub>, 0 °C) δ -119.25 (m, 0.60 F), -119.35 (m, 0.40 F) ppm; IR (CH<sub>2</sub>Cl<sub>2</sub>) 3295, 1700, 1684 cm<sup>-1</sup>; Anal. Calcd for C<sub>20</sub>H<sub>21</sub>FN<sub>2</sub>O<sub>3</sub>: C, 67.40; H, 5.94; N, 7.86. Found: C, 67.72; H, 5.99; N, 8.01.

**2-[(4-Nitrophenyl)amino]carbonyl]-1-pyrrolidinecarboxylic acid phenylmethyl ester (**1i**).** CBZ-Proline and 4-nitroaniline were coupled by a procedure analogous to that used for **1e**, and recrystallization from CH<sub>2</sub>Cl<sub>2</sub>/pentane provided 72% of **1i** as a yellow solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 0 °C) δ 10.0 (s, 0.9 H), 8.4 (s, 0.1 H), 8.1 (d, 0.2 H), 8.0 (d, 1.8 H), 7.5 (d, 1.8 H), 7.5-7.3 (m, 5.2 H), 5.3 (dd, 2 H), 4.6 (dd, 0.9 H), 4.5 (m, 0.1 H), 3.7 (m, 1 H), 3.5 (m, 0.9 H), 3.1 (m, 0.1 H), 2.3 (m, 1 H), 2.2-2.0 (m, 2 H), 1.9 (m, 1 H) ppm; <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>, 0 °C) δ 170.7, 156.3, 144.0, 142.6, 136.0, 128.5, 128.2, 127.8, 124.5, 118.7, 67.7, 67.6, 60.9, 60.8, 47.2, 28.6, 24.5 ppm; IR (CH<sub>2</sub>Cl<sub>2</sub>) 3290, 1708, 1673 cm<sup>-1</sup>; Anal. Calcd for C<sub>19</sub>H<sub>19</sub>N<sub>3</sub>O<sub>5</sub>: C, 61.78; H, 5.18; N, 11.38. Found: C, 61.66; H, 5.11; N, 11.25.

**2-[(4-Methoxyphenyl)amino]carbonyl]-1-pyrrolidinecarboxylic acid phenylmethyl ester (**1j**).** CBZ-Proline and 4-anisidine were coupled by a procedure analogous to that used for **1e**, and recrystallization from EtOAc/hexanes yielded 43% of **1j** as a beige solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 0 °C) δ 9.1 (s, 0.7 H), 7.8 (s, 0.3 H), 7.4-7.2 (m, 7 H), 6.8 (m, 2 H), 5.2-5.0 (m, 2 H), 4.5 (d, 0.7 H), 3.82 (s, 0.9 H), 3.80 (s, 2.1 H), 3.6-3.5 (m, 1.3 H), 3.4 (m, 0.7 H), 2.5 (m, 1 H), 2.2 (m, 1 H), 2.1-1.9 (m, 2 H) ppm; <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>, 0 °C) δ 169.2, 156.6, 155.8, 136.1, 131.2, 128.5, 128.2, 128.0, 127.9, 121.7, 121.1, 121.0, 113.8, 113.7, 67.5, 67.4, 61.4, 60.8, 55.3, 47.7, 47.0, 31.0, 27.6, 24.6, 23.7 ppm; IR (CH<sub>2</sub>Cl<sub>2</sub>) 3290, 1691 (2 unresolved stretches) cm<sup>-1</sup>; Anal. Calcd for C<sub>20</sub>H<sub>22</sub>N<sub>2</sub>O<sub>4</sub>: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.68; H, 6.29; N, 7.84.

**1-Acetyl-N-[(3-fluorophenyl)methyl]-2-pyrrolidinecarboxamide (**1k**).** N-Acetylproline and 3-fluorobenzylamine were coupled by Procedure A and chromatography with 50-100% EtOAc/hexanes yielded 65% of **1k** as a white solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.7 (s, 0.9 H), 7.3-6.9 (m, 4.1 H), 4.6 (dd, 0.9 H), 4.5-4.3 (m, 2.1 H), 3.6-3.4 (m, 2 H), 2.5 (m, 1 H), 2.2-2.0 (m, 1 H), 2.1 (s, 2.7 H), 2.0 (m, 1 H), 1.9 (s, 0.3 H), 1.8 (m, 1 H) ppm; <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 171.8, 171.2, 171.0, 170.4, 163.8, 161.9, 141.1, 141.0, 130.2, 130.1, 130.0, 129.9, 123.0, 122.8, 122.7, 114.4, 114.3, 114.2, 114.0, 113.8, 62.3, 59.5, 48.2, 46.6, 42.8, 42.7, 42.6, 32.0, 27.3, 25.0, 22.8, 22.4, 22.3 ppm; IR (CH<sub>2</sub>Cl<sub>2</sub>) 3307, 1658, 1634 cm<sup>-1</sup>; Anal. Calcd for C<sub>14</sub>H<sub>17</sub>FN<sub>2</sub>O<sub>2</sub>: C, 63.62; H, 6.48; N, 10.60. Found: C, 63.36; H, 6.47; N, 10.47.

**1-(2-Fluorobenzoyl)-proline hexyl ester (**2a**).** Proline **15** and hexanol were coupled by Procedure A and chromatography with 10-25% EtOAc/hexanes yielded 61% of **2a** as a colorless oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.5-7.3 (m, 2 H), 7.2-7.0 (m, 2 H), 4.7 (dd, 0.75 H), 4.3 (dd, 0.25 H), 4.2-4.1 (m, 1.75 H), 4.0-3.8 (m,

0.5 H), 3.6-3.4 (m, 1.75 H), 2.4-2.3 (m, 1 H), 2.1-1.9 (m, 3 H), 1.7 (m, 2 H), 1.5-1.1 (m, 6 H), 0.9 (m, 3 H) ppm;  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  171.7, 171.6, 165.3, 165.0, 159.3, 158.9, 156.9, 156.4, 131.3, 131.2, 131.1, 131.0, 129.0, 128.9, 128.8, 128.7, 124.8, 124.7, 124.6, 124.5, 124.2, 124.1, 115.7, 115.5, 115.4, 65.2, 65.1, 60.1, 58.8, 48.0, 47.9, 46.3, 31.2, 31.1, 31.0, 29.4, 28.3, 28.1, 25.3, 25.1, 24.5, 22.6, 22.3, 22.3, 13.8 ppm;  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -115.0 (m, 0.75 F), -115.6 (m, 0.25 F) ppm; IR (neat) 1738, 1646  $\text{cm}^{-1}$ ; HRMS (EI) calcd mass 321.1740. Found: 321.1738. Anal. Calcd for  $\text{C}_{18}\text{H}_{24}\text{FNO}_3$ : C, 67.27; H, 7.53; N, 4.36. Found: C, 67.15; H, 7.58; N, 4.28.

**1-Acetylproline phenyl ester (2b).** N-Acetylproline and phenol were coupled by Procedure A and chromatography with 10-50% EtOAc/hexanes yielded 64% of **2b** as a colorless oil which solidified upon standing.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.4-7.0 (m, 5 H), 4.7 (dd, 0.8 H), 4.6 (dd, 0.2 H), 3.7-3.5 (m, 2 H), 2.3 (m, 1 H), 2.2-2.0 (m, 3 H), 2.10 (s, 2.4 H), 2.08 (s, 0.6 H) ppm;  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  171.0, 169.4, 150.6, 129.6, 129.2, 126.2, 125.7, 121.3, 120.9, 60.2, 58.7, 47.7, 46.4, 31.6, 29.4, 24.9, 22.8, 22.2 ppm; IR (KBr) 1750, 1638  $\text{cm}^{-1}$ ; HRMS (EI) calcd mass 233.1052. Found: 233.1053. Anal. Calcd for  $\text{C}_{13}\text{H}_{15}\text{NO}_3$ : C, 66.94; H, 6.48; N, 6.00. Found: C, 66.71; H, 6.55; N, 5.92.

**1-Acetylproline 4-methoxyphenyl ester (2c).** N-Acetylproline and 4-methoxyphenol were coupled by Procedure A and chromatography with 25-100% EtOAc/hexanes yielded 77% of **2c** as a white solid.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.1-7.0 (m, 2 H), 6.9 (m, 2 H), 4.7 (dd, 0.8 H), 4.6 (dd, 0.2 H), 3.80 (s, 0.6 H), 3.78 (s, 2.4 H), 3.7 (m, 1 H), 3.5 (m, 1 H), 2.4 (m, 1 H), 2.2-2.0 (m, 3 H), 2.10 (s, 2.4 H), 2.05 (s, 0.6 H) ppm;  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  171.3, 169.4, 157.2, 144.1, 122.1, 121.7, 114.5, 114.3, 60.1, 58.7, 55.5, 47.7, 46.3, 31.6, 29.4, 24.9, 22.8, 22.2 ppm; IR (KBr) 1753, 1638  $\text{cm}^{-1}$ ; HRMS (EI) calcd mass 263.1158. Found: 263.1159. Anal. Calcd for  $\text{C}_{14}\text{H}_{17}\text{NO}_4$ : C, 63.87; H, 6.51; N, 5.32. Found: C, 64.03; H, 6.61; N, 5.31.

**1-Acetylproline 4-(dimethylamino)phenyl ester (2d).** N-Acetylproline and 4-N,N-dimethylaminophenol<sup>1</sup> were coupled by Procedure A and chromatography with 25-75% EtOAc/hexanes yielded 73% of **2d** as an off-white solid.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.0 (m, 2 H), 6.7 (m, 2 H), 4.7 (dd, 0.75 H), 4.6 (dd, 0.25 H), 3.7-

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<sup>1</sup> Wagener, C. C. P.; Modro, A. M.; Modro, T. A. *J. Phys. Org. Chem.* **1991**, 4, 516.

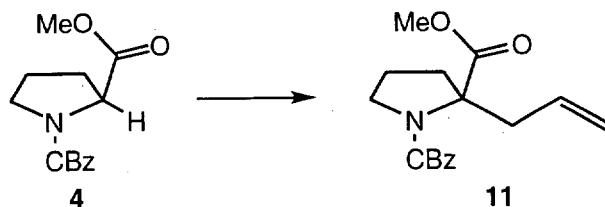
3.5 (m, 2 H), 2.95 (s, 1.5 H), 2.90 (s, 4.5 H), 2.4-2.3 (m, 1 H), 2.2-2.1 (m, 2 H), 2.15 (s, 2.25 H), 2.10 (s, 0.75), 2.1-2.0 (m, 1 H) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  171.5, 169.3, 148.6, 141.5, 121.6, 121.2, 112.9, 112.8, 94.7, 60.2, 58.7, 47.7, 46.3, 40.9, 40.7, 31.6, 29.4, 24.8, 22.8, 22.3, 22.2 ppm; IR ( $\text{CH}_2\text{Cl}_2$ ) 1760, 1647  $\text{cm}^{-1}$ ; Anal. Calcd for  $\text{C}_{15}\text{H}_{20}\text{N}_2\text{O}_3$ : C, 65.20; H, 7.30; N, 10.14. Found: C, 65.02; H, 7.27; N, 10.04.

**1-Acetylproline 4-(methoxycarbonyl)phenyl ester (2e).** N-Acetylproline and methyl 4-hydroxybenzoate were coupled by Procedure A and chromatography with 25-100% EtOAc/hexanes yielded 67% of **2e** as a pale yellow oil.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.1 (m, 2 H), 7.2 (m, 2 H), 4.6 (m, 1 H), 3.95 (s, 0.3 H), 3.9 (s, 2.7 H), 3.7 (m, 1 H), 3.6 (m, 1 H), 2.4 (m, 1 H), 2.2-2.0 (m, 3 H), 2.15 (s, 2.7 H), 2.10 (s, 0.3 H) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  170.4, 170.1, 169.5, 166.1, 165.9, 154.2, 153.6, 131.1, 130.9, 127.5, 121.4, 121.0, 60.0, 58.7, 58.6, 52.1, 52.0, 47.6, 46.2, 31.4, 29.3, 24.8, 22.7, 22.2, 22.0 ppm; IR (neat) 1766, 1721, 1650  $\text{cm}^{-1}$ ; Anal. Calcd for  $\text{C}_{15}\text{H}_{17}\text{NO}_5$ : C, 61.85; H, 5.88; N, 4.81. Found: C, 61.72; H, 5.95; N, 4.87.

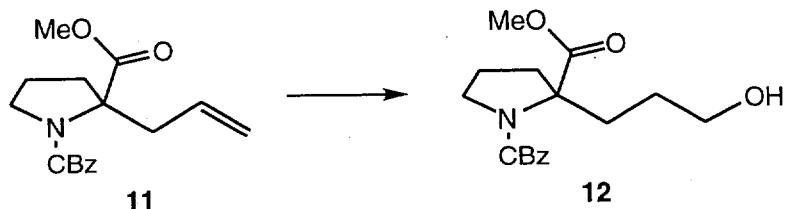
**2-[(2-Fluorophenyl)methyl]-1-(phenylmethyl)-1,2-pyrrolidinedicarboxylic acid ester (2g).** CBZ-Proline and 2-fluorobenzyl alcohol were coupled by Procedure A and chromatography with 10-25% EtOAc/hexanes yielded 65% of **2g** as a colorless oil.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.4-7.0 (m, 9 H), 5.4-5.0 (m, 4 H), 4.5 (dd, 0.45 H), 4.4 (dd, 0.55 H), 3.6 (m, 1 H), 3.5-3.4 (m, 1 H), 2.2 (m, 1 H), 2.1-1.8 (m, 3 H) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  172.5, 172.3, 161.7, 159.7, 154.7, 154.1, 136.4, 136.3, 130.4, 130.37, 130.35, 130.34, 130.30, 130.2, 130.1, 128.3, 128.2, 127.9, 127.8, 127.7, 127.6, 124.1, 124.05, 124.0, 122.6, 122.5, 122.4, 122.3, 115.4, 115.3, 115.2, 66.9, 66.8, 66.7, 60.8, 60.7, 60.6, 59.0, 58.7, 46.8, 46.3, 30.8, 29.8, 24.1, 23.4 ppm;  $^{19}\text{F}$  NMR (470 MHz,  $\text{CDCl}_3$ )  $\delta$  -118.30 (m, 0.55 F), -118.35 (m, 0.45 F) ppm; IR (neat) 1748, 1704  $\text{cm}^{-1}$ ; Anal. Calcd for  $\text{C}_{20}\text{H}_{20}\text{FNO}_4$ : C, 67.22; H, 5.64; N, 3.92. Found: C, 67.22; H, 5.69; N, 3.96.

**2-Phenyl-1-(phenylmethyl)-1,2-pyrrolidinedicarboxylic acid ester (2h).** CBZ-Proline and phenol were coupled by Procedure A and chromatography with 25% EtOAc/hexanes yielded 52% of **2h** as a colorless oil which solidified upon standing.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ , 0 °C)  $\delta$  7.4-7.1 (m, 9 H), 6.8 (m, 1 H), 5.3-5.0 (m, 2 H), 4.6 (dd, 0.4 H), 4.55 (dd, 0.6 H), 3.8-3.5 (m, 2 H), 2.4 (m, 1 H), 2.2 (m, 1 H), 2.1-2.0 (m, 2 H) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ , 0 °C)  $\delta$  171.4, 171.3, 154.8, 154.2, 150.4, 150.1, 136.4, 136.2, 129.3, 128.5, 128.4, 128.1, 128.0, 127.9, 127.8, 125.9, 125.8, 121.3, 121.1, 67.2, 67.0, 59.3, 58.8, 47.0, 46.4, 31.0, 30.0, 24.4, 23.6

ppm;  $^{19}\text{F}$  NMR (470 MHz,  $\text{CDCl}_3$ , 0 °C) δ -119.25 (m, 0.60 F), -119.35 (m, 0.40 F) ppm; IR ( $\text{CH}_2\text{Cl}_2$ ) 1768, 1704  $\text{cm}^{-1}$ ; Anal. Calcd for  $\text{C}_{19}\text{H}_{19}\text{NO}_4$ : C, 70.14; H, 5.89; N, 4.30. Found: C, 70.06; H, 5.87; N, 4.32.

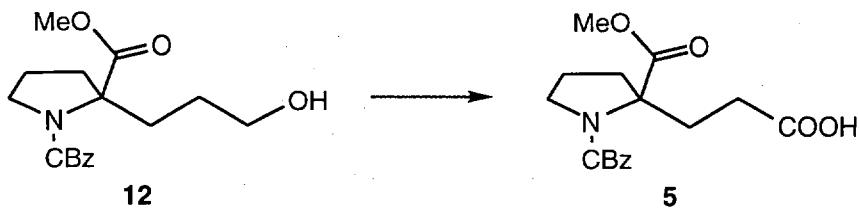


**2-(2-Propenyl)-1,2-pyrrolidinedicarboxylic acid 2-methyl 1-(phenylmethyl) ester (11).** To 24.0 mL (114 mmol) 1,1,1,3,3,3-hexamethyldisilazane stirring in 150 mL THF at -78 °C was slowly added 71.3 mL of 1.6 M butyllithium (114 mmol, in hexanes). This solution was stirred for 15 min and then slowly cannulated into a solution of 25 g (95 mmol) CBZ-L-proline methyl ester (**4**) in 100 mL of THF at -78 °C. The resulting mixture was stirred for 15 min and then 10.7 mL (124 mmol) allyl bromide (freshly purified by passing through a plug of Brockmann I activated basic alumina) was added slowly over a period of 10 min. The solution was allowed to warm to rt and stirring was continued for 3 h before quenching with 100 mL 1.0 M HCl and removal of THF by rotary evaporation. An additional 100 mL 1.0 M HCl was added and the acidic solution was extracted with diethyl ether (3 x 100 mL). The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$  and the solvent was evaporated. The crude material was purified by flash column chromatography with 5-20% EtOAc/hexanes to yield 26.5 g (92%) of **11** as a colorless oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) δ 7.4-7.2 (m, 5 H), 5.8-5.6 (m, 1 H), 5.2-5.0 (m, 4 H), 3.8-3.6 (m, 1 H), 3.7 (s, 1.7 H), 3.5-3.4 (m, 1 H), 3.5 (s, 1.3 H), 3.1 (dd, 0.55 H), 2.9 (dd, 0.45 H), 2.7-2.6 (m, 1 H), 2.2-2.0 (m, 2 H), 1.9-1.8 (m, 2 H) ppm;  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ) δ 174.3, 174.2, 153.9, 136.7, 136.1, 132.9, 132.6, 128.1, 128.0, 127.9, 127.7, 127.5, 127.3, 118.9, 118.8, 67.8, 66.9, 66.8, 66.3, 52.1, 51.9, 48.9, 48.1, 39.2, 37.8, 36.8, 35.3, 22.9, 22.4 ppm; IR (neat) 1741, 1704, 1640  $\text{cm}^{-1}$ ; Anal. Calcd for  $\text{C}_{17}\text{H}_{21}\text{NO}_4$ : C, 67.31; H, 6.98; N, 4.62. Found: C, 67.36; H, 7.06; N, 4.60.



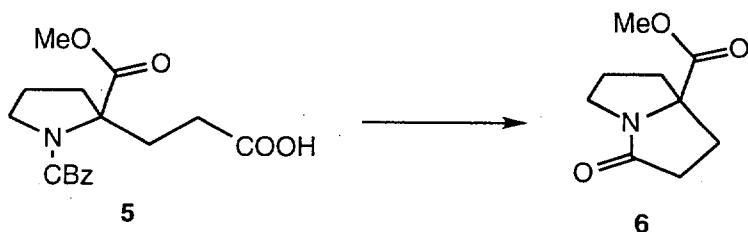
**2-(3-Hydroxypropyl)-1,2-pyrroldinedicarboxylic acid 2-methyl 1-(phenylmethyl) ester (12).**

Disiamylborane was prepared by the slow addition of 30 mL of 2.0 M 2-methyl-2-butene (60 mmol, in THF) to 30 mL of 1.0 M  $\text{BH}_3\cdot\text{THF}$  (60 mmol) stirring at 0 °C. After the resulting mixture had stirred for 2.5 h, 9.0 g (30 mmol) of **11** was dissolved in 25 mL THF and added to the disiamylborane solution. The mixture was warmed to rt and allowed to stir 5 h before adding 11 mL 3.0 M NaOH, followed by careful addition of 11 mL 30%  $\text{H}_2\text{O}_2$ . The reaction was stirred for 0.5 h longer and then quenched by the addition of 100 mL saturated brine. The organic layer was removed and the aqueous phase was extracted with diethyl ether (3 x 100 mL). The organic layers were combined, dried with  $\text{Na}_2\text{SO}_4$ , and then concentrated. The crude material was purified by flash column chromatography with 25-90% EtOAc/hexanes to yield 8.37 g (87%) of **12** as a colorless oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) δ 7.3 (m, 5 H), 5.2-5.0 (m, 2 H), 3.8-3.4 (m, 4 H), 3.7 (s, 1.7 H), 3.5 (s, 1.3 H), 2.5 (bs, 1 H), 2.3 (m, 1 H), 2.1-1.8 (m, 5 H), 1.7-1.4 (m, 2 H) ppm;  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ) δ 174.8, 174.6, 154.3, 154.2, 136.6, 136.1, 128.2, 128.1, 128.0, 127.9, 127.6, 127.4, 68.3, 67.4, 66.9, 66.5, 62.4, 62.3, 52.2, 52.0, 49.0, 48.3, 37.3, 35.9, 31.1, 30.0, 26.8, 26.7, 23.0, 22.5 ppm; IR (neat) 3451, 1738, 1696  $\text{cm}^{-1}$ ; HRMS (EI) calcd mass 321.1576. Found: 321.1575. Anal. Calcd for  $\text{C}_{17}\text{H}_{23}\text{NO}_5$ : C, 63.54; H, 7.21; N, 4.36. Found: C, 63.66; H, 7.29; N, 4.33.

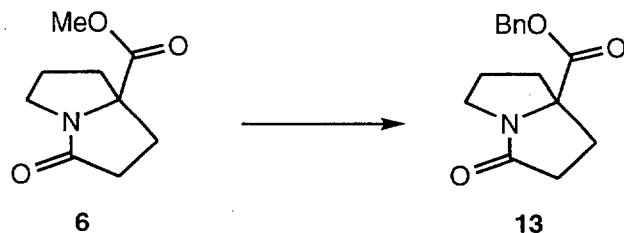
**2-(2-Carboxyethyl)-1,2-pyrrolidinedicarboxylic acid 2-methyl 1-(phenylmethyl) ester (5).**

A solution of 15.9 g (49.5 mmol) of **12** in 400 mL acetone was added dropwise over a 4 h period to 15 g (150 mmol)  $\text{CrO}_3$  dissolved in 250 mL of 1.5 M  $\text{H}_2\text{SO}_4$  stirring at 0 °C. When the addition was complete, the solution was brought to rt and stirred for 1.5 h before quenching with 150 mL water. Enough NaCl to saturate the solution was added with stirring, the insoluble salt was filtered off, and the mixture was extracted with 300 mL diethyl ether. The aqueous layer was extracted with ether (3 x 100 mL), the organic layers were combined and the solvent was evaporated. The crude material was redissolved in 250 mL  $\text{CH}_2\text{Cl}_2$  and washed with saturated brine (2 x 100 mL). The organic layer was dried with  $\text{Na}_2\text{SO}_4$ , concentrated to approximately 25 mL, and the

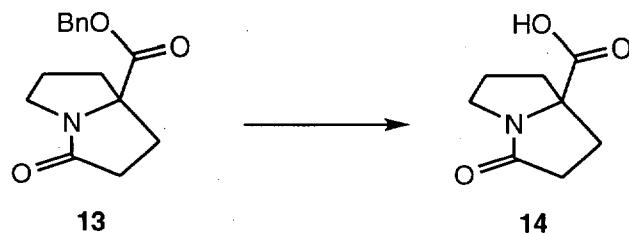
viscous solution was run through a plug of silica to remove the remaining chromium byproducts. The eluant was concentrated and the crude material was recrystallized from CH<sub>2</sub>Cl<sub>2</sub>/pentane to yield 9.8 g (59%) of **5** as a white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 11.2 (s, 1 H), 7.3 (m, 5 H), 5.2-5.0 (m, 2 H), 3.8 (m, 1 H), 3.7 (s, 1.7 H), 3.5 (m, 1 H), 3.4 (s, 1.3 H), 2.6 (m, 1 H), 2.5-2.4 (m, 2 H), 2.4-2.4 (m, 2 H), 2.1 (m, 1 H), 2.0-1.8 (m, 2 H) ppm; <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 178.7, 178.4, 174.2, 174.0, 154.6, 154.4, 136.6, 136.0, 128.5, 128.4, 128.35, 128.30, 128.1, 127.9, 127.6, 67.9, 67.3, 67.1, 66.9, 52.4, 52.2, 49.1, 48.3, 37.4, 36.3, 30.0, 29.4, 29.2, 29.0, 23.1, 22.7 ppm; IR (neat) 3080, 1738, 1702, 1654 cm<sup>-1</sup>; HRMS (EI) calcd mass 335.1369. Found: 335.1368. Anal. Calcd for C<sub>17</sub>H<sub>21</sub>NO<sub>6</sub>: C, 60.89; H, 6.31; N, 4.18. Found: C, 60.95; H, 6.36; N, 4.07.



**Tetrahydro-3-oxo-1H-pyrrolizine-7a(5H)-carboxylic acid methyl ester (6).** A solution of 9.7 g (29 mmol) of **5** dissolved in 100 mL of a 50:50 mixture of MeOH and EtOAc containing a catalytic amount of 10% Pd on activated carbon was stirred under H<sub>2</sub> at atmospheric pressure for 3 h. The insoluble material was then filtered by passing the reaction mixture through a plug of Celite 545® with the aid of additional MeOH, and the filtrate was concentrated by rotary evaporation. After removing all traces of solvent under vacuum, the residue was dissolved in 100 mL CH<sub>2</sub>Cl<sub>2</sub> with 5.6 g (29 mmol) EDCI and the mixture was stirred at rt for 12 h. The reaction mixture was washed with 1.0 M HCl (3 × 100 mL) and the organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>. Concentration by rotary evaporation yielded 4.2 g (79%) of **6** as an analytically pure colorless oil which formed an off-white solid upon standing open to air. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.8 (s, 3 H), 3.7-3.6 (m, 1 H), 3.2-3.1 (m, 1 H), 2.8 (m, 1 H), 2.5 (m, 1 H), 2.4 (m, 2 H), 2.1-2.0 (m, 3 H), 1.7 (m, 1 H) ppm; <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 174.9, 174.1, 73.5, 52.6, 41.6, 36.0, 34.3, 31.7, 26.0 ppm; IR (KBr) 1738, 1682 cm<sup>-1</sup>; HRMS (EI) calcd mass 183.0895. Found: 183.0896. Anal. Calcd for C<sub>9</sub>H<sub>13</sub>NO<sub>3</sub>: C, 59.00; H, 7.15; N, 7.65. Found: C, 58.94; H, 7.22; N, 7.55.

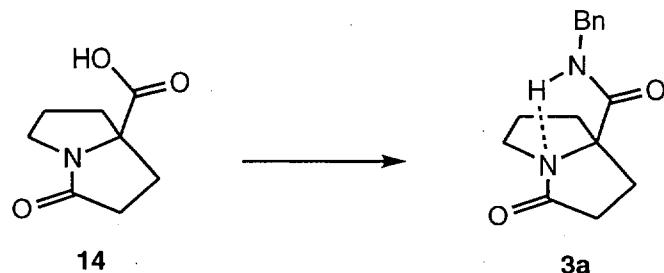


**Tetrahydro-3-oxo-1H-pyrrolizine-7a(5H)-carboxylic acid benzyl ester (13).** A titanate-mediated transesterification<sup>2</sup> was carried out by dissolving 3.4 g (18.6 mmol) **6** and 2.05 mL (7 mmol)  $\text{Ti}(\text{i-OPr})_4$  in 120 mL benzyl alcohol and heating to 110 °C for 15 h. The benzyl alcohol was removed by distillation under vacuum, and the residue was purified by flash column chromatography with 10-50%  $\text{EtOAc}/\text{hexane}$  to yield 3.9 g (81%) of **13** as a white solid.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.4 (m, 5 H), 5.2 (s, 2 H), 3.7 (m, 1 H), 3.2 (m, 1 H), 2.8 (m, 1 H), 2.6 (m, 1 H), 2.5 (m, 2 H), 2.1-2.0 (m, 3 H), 1.7 (m, 1 H) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  174.9, 173.5, 135.3, 128.6, 128.5, 128.0, 73.6, 67.2, 41.6, 36.0, 34.3, 31.6, 26.0 ppm; IR ( $\text{CH}_2\text{Cl}_2$ ) 1735, 1694  $\text{cm}^{-1}$ ; HRMS (CI) calcd mass for  $\text{C}_{15}\text{H}_{17}\text{NO}_3$  ( $M + 1$ ): 260.1208. Found: 260.1289.



**Tetrahydro-3-oxo-1H-pyrrolizine-7a(5H)-carboxylic acid (14).** A solution of 1.1 g (4.2 mmol) of **13** dissolved in 20 mL of a 50:50 mixture of  $\text{MeOH}$  and  $\text{EtOAc}$  containing a catalytic amount of 10% Pd on activated carbon was stirred under  $\text{H}_2$  at atmospheric pressure for 3 h. The insoluble material was then filtered by passing the reaction mixture through a plug of Celite 545® with the aid of additional  $\text{MeOH}$ , and the filtrate was concentrated by rotary evaporation to yield 655 mg (92%) of **14** as a white solid.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  11.5 (s, 1 H), 3.7 (m, 1 H), 3.2 (m, 1 H), 2.9 (m, 1 H), 2.6-2.5 (m, 3 H), 2.1 (m, 3 H), 1.7 (m, 1 H) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  176.2, 175.7, 73.9, 41.4, 35.7, 34.4, 31.6, 25.9 ppm; IR ( $\text{CH}_2\text{Cl}_2$ ) 3000, 1694, 1647  $\text{cm}^{-1}$ ; HRMS (EI) calcd mass for  $\text{C}_8\text{H}_{11}\text{NO}_3$ : 169.0739. Found: 169.0742.

2 Seebach, D.; Hungerbühler, E.; Naef, R.; Schnurrenberger, P.; Weidmann, B.; Züger, M. *Synthesis* **1982**, 138.



**Tetrahydro-3-oxo-N-(phenylmethyl)-1H-pyrrolizine-7a(5H)-carboxamide (3a).** Procedure A, employing 300 mg (1.8 mmol) **14**, 0.20 mL (1.8 mmol) benzylamine, and 375 mg (2.0 mmol) EDCI, followed by purification by flash column chromatography with 50-90% EtOAc/hexanes yielded 344 mg (75%) of **3a** as a white solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.4-7.2 (m, 5 H), 7.1 (s, 1 H), 4.6-4.4 (m, 2 H), 3.6 (m, 1 H), 3.1 (m, 1 H), 2.7 (m, 1 H), 2.6-2.5 (m, 2 H), 2.4 (m, 1 H), 2.2 (m, 1 H), 2.0-1.9 (m, 2 H), 1.7 (m, 1 H) ppm; <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 178.0, 173.6, 138.0, 128.7, 127.6, 127.5, 74.7, 43.5, 43.0, 36.2, 33.6, 32.2, 25.9 ppm; IR (CH<sub>2</sub>Cl<sub>2</sub>) 3416, 1702, 1672 cm<sup>-1</sup>; Anal. Calcd for C<sub>15</sub>H<sub>18</sub>N<sub>2</sub>O<sub>2</sub>: C, 69.74; H, 7.02; N 10.84. Found: C, 69.80; H, 6.97; N, 10.62.

**Procedure B. Synthesis of Tetrahydro-N-(4-methoxyphenyl)-3-oxo-1H-pyrrolizine-7a(5H)-carboxamide (3c).** The following representative example of a Bodroux reaction<sup>3</sup> was employed for the direct conversion of methyl ester **6** to locked amide anilides **3b-3f**. To 1.35 g (11 mmol) 4-anisidine stirring at rt in 20 mL THF was slowly added 3.6 mL of 3.0 M MeMgBr (11 mmol, in ether). After 5 min, 1.0 g (5.5 mmol) of **6** dissolved in 5 mL THF was added to the reaction mixture, and the solution was stirred at rt for 5 h. The solution was quenched with 50 mL 1.0 M HCl, the THF was removed by rotary evaporation, and the aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 50 mL). After concentration, the residue was purified by recrystallization from CH<sub>2</sub>Cl<sub>2</sub>/hexanes to yield 1.06 g (71%) of **3c** as a white solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.4 (s, 1 H), 7.5 (m, 2 H), 6.9 (m, 2 H), 3.8 (s, 3 H), 3.7 (m, 1 H), 3.2 (m, 1 H), 2.8 (m, 1 H), 2.7-2.6 (m, 2 H), 2.5 (m, 1 H), 2.2 (m, 1 H), 2.1-2.0 (m, 2 H), 1.7 (m, 1 H) ppm; <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 178.6, 171.9, 156.7, 130.4,

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3 Basset, H. L.; Thomas, C. R. *J. Chem. Soc.* **1954**, 1188.

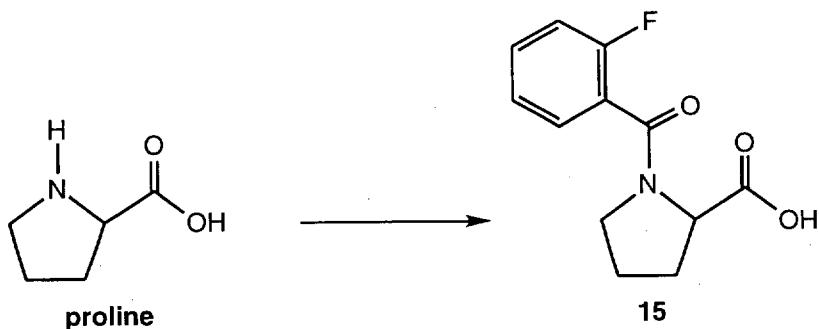
121.7, 114.1, 75.0, 55.5, 43.4, 36.4, 33.5, 32.1, 25.8 ppm; IR ( $\text{CH}_2\text{Cl}_2$ ) 3387, 1705, 1681  $\text{cm}^{-1}$ ; Anal. Calcd for  $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_3$ : C, 65.68; H, 6.61; N 10.21. Found: C, 65.40; H, 6.60; N, 10.04.

**N-[4-(Dimethylamino)phenyl]tetrahydro-3-oxo-1*H*-pyrrolizine-7*a*(5*H*)-carboxamide (3b).** Procedure B was used with slight modifications: 1) To soak up the excess HCl present in the amino component (N,N-dimethyl-1,4-phenylenediamine dihydrochloride), 6 equiv of BuLi was employed; 2) the reaction was carried out in the dark; and 3) the reaction could not be worked up with acid, so the wash was limited to saturated  $\text{NaHCO}_3$ . Concentration, followed by flash column chromatography with 50-100% EtOAc/hexanes, and then recrystallization from  $\text{CH}_2\text{Cl}_2$ /pentane provided 53% of **3b** as a white solid.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.0 (s, 1 H), 7.4 (d, 2 H), 6.7 (d, 2 H), 3.8 (m, 1 H), 3.2 (m, 1 H), 2.9 (s, 6 H), 2.8 (m, 1 H), 2.6 (m, 2 H), 2.5 (m, 1 H), 2.2 (m, 1 H), 2.0 (m, 2 H), 1.7 (m, 1 H) ppm;  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  178.8, 171.5, 148.2, 126.7, 121.4, 112.9, 95.5, 95.4, 75.0, 43.6, 40.9, 36.5, 33.6, 32.2, 25.9 ppm; IR ( $\text{CH}_2\text{Cl}_2$ ) 3392, 1701, 1676  $\text{cm}^{-1}$ ; Anal. Calcd for  $\text{C}_{16}\text{H}_{21}\text{N}_3\text{O}_2$ : C, 66.88; H, 7.37; N 14.62. Found: C, 66.67; H, 7.42; N, 14.49.

**N-(4-Bromophenyl)tetrahydro-3-oxo-1*H*-pyrrolizine-7*a*(5*H*)-carboxamide (3d).** Procedure B, followed by recrystallization from  $\text{CH}_2\text{Cl}_2$ /hexanes provided 80% of **3d** as a white solid.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.7 (s, 1 H), 7.6 (d, 2 H), 7.5 (d, 2 H), 3.7 (m, 1 H), 3.2 (m, 1 H), 2.8 (m, 1 H), 2.7-2.6 (m, 2 H), 2.5 (m, 1 H), 2.3 (m, 1 H), 2.1-2.0 (m, 2 H), 1.7 (m, 1 H) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  178.5, 172.4, 136.5, 131.9, 131.8, 121.6, 117.4, 75.1, 43.4, 36.5, 33.6, 32.1, 25.8 ppm; IR (KBr) 3296, 1701, 1678  $\text{cm}^{-1}$ ; HRMS (EI) calcd mass 322.0317; found 322.0312. Anal. Calcd for  $\text{C}_{14}\text{H}_{15}\text{BrN}_2\text{O}_2$ : C, 52.03; H, 4.68; N 8.67. Found: C, 51.99; H, 4.56; N, 8.61.

**4-[[Tetrahydro-3-oxo-1*H*-pyrrolizin-7*a*(5*H*)-yl]carbonyl]amino]-benzoic acid methyl ester (3e).** Procedure B (with a 5 h reflux period) followed by recrystallization first from  $\text{CH}_2\text{Cl}_2$ /hexanes, then from  $\text{CH}_2\text{Cl}_2$ /ether provided 49% of **3e** as a white solid.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.5 (s, 1 H), 8.1 (d, 2 H), 7.7 (d, 2 H), 3.9 (s, 3 H), 3.8 (m, 1 H), 3.2 (m, 1 H), 2.8 (m, 1 H), 2.7-2.6 (m, 2 H), 2.5 (m, 1 H), 2.3 (m, 1 H), 2.1-2.0 (m, 2 H), 1.8 (m, 1 H) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  179.0, 172.7, 166.4, 141.2, 130.8, 128.3, 126.3, 119.1, 94.8, 75.1, 52.1, 43.8, 36.5, 33.4, 32.0, 25.8 ppm; IR ( $\text{CH}_2\text{Cl}_2$ ) 3381, 1716, 1693  $\text{cm}^{-1}$ ; Anal. Calcd for  $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}_4$ : C, 63.65; H, 6.00; N 9.27. Found: C, 63.52; H, 5.97; N, 9.32.

**Tetrahydro-N-(4-nitrophenyl)-3-oxo-1H-pyrrolizine-7a(5H)-carboxamide (3f).** Procedure B (with a 5 h reflux period) followed by recrystallization from CH<sub>2</sub>Cl<sub>2</sub>/hexanes provided 627 mg (40%) of **3f** as a beige solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 9.4 (s, 1 H), 8.2 (d, 2 H), 8.0 (d, 2 H), 3.7 (m, 1 H), 3.2 (m, 1 H), 2.9 (m, 1 H), 2.7 (m, 1 H), 2.6 (m, 1 H), 2.5 (m, 1 H), 2.3 (m, 1 H), 2.1 (m, 1 H), 2.0 (m, 1 H), 1.8 (m, 1 H) ppm; <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 178.4, 173.2, 143.8, 143.5, 124.9, 119.8, 75.3, 43.3, 36.5, 33.7, 32.1, 25.8 ppm; IR (CH<sub>2</sub>Cl<sub>2</sub>) 3376, 1698 (2 unresolved stretches) cm<sup>-1</sup>; Anal. Calcd for C<sub>14</sub>H<sub>15</sub>N<sub>3</sub>O<sub>4</sub>: C, 58.13; H, 5.23; N 14.53. Found: C, 58.03; H, 5.28; N, 14.46.



**1-(2-Fluorobenzoyl)-proline (15).** To 6.43 g (55.8 mmol) proline and 15.6 mL (112 mmol) triethylamine stirring in 150 mL THF at 0 °C was added 10 mL (83.7 mmol) 2-fluorobenzoyl chloride. The mixture was allowed to warm to rt and stir overnight. To the reaction mixture was added 50 mL 3.0 M KOH and stirring was continued for 4 h. The mixture was added to a separatory funnel and the bottom aqueous phase was removed and acidified with concentrated HCl. The organic phase was concentrated by rotary evaporation, the residue was dissolved in 200 mL EtOAc, and was mixed with the previously acidified aqueous phase. This mixture was then added to the separatory funnel, the aqueous layer was removed, and then extracted with EtOAc (3 x 100 mL). The combined organic layers were dried with Na<sub>2</sub>SO<sub>4</sub> and concentrated to approximately 50 mL. This viscous mixture was diluted with 100 mL diethyl ether, placed in the freezer overnight, and yielded 8.3 g of **15** as a white solid. The filtrate was diluted with 100 mL ether and placed in the freezer overnight to provide 1.2 g more material (72% combined yield). <sup>1</sup>H NMR (400 MHz, d<sub>3</sub>-MeOD) δ 7.4-7.0 (m, 4 H), 4.4 (dd, 0.7 H), 4.1 (dd, 0.3 H), 3.6-3.5 (m, 0.6 H), 3.4-3.2 (m, 1.4 H), 2.3-2.1 (m, 1 H), 2.0-1.7 (m, 3 H) ppm; <sup>13</sup>C NMR (101 MHz, d<sub>3</sub>-MeOD) δ 175.0, 168.0, 167.5, 160.9, 158.4, 133.2, 133.1, 130.1, 130.0, 129.8, 129.7, 125.85, 125.80, 117.1, 117.0, 116.9, 116.8, 62.0, 60.3, 47.7, 32.2, 30.7, 25.7, 23.7 ppm; <sup>19</sup>F NMR (376

MHz, d<sub>3</sub>-MeOD) δ -115.3 (m, 0.8 F), -115.7 (m, 0.2 F) ppm; IR (KBr) 2930, 1741, 1612 cm<sup>-1</sup>; HRMS (EI) calcd mass 237.0801. Found: 237.0802. Anal. Calcd for C<sub>12</sub>H<sub>12</sub>FNO<sub>3</sub>: C, 60.76; H, 5.10; N, 5.90. Found: C, 60.69; H, 5.11; N, 5.86.