# Enantioselective Molecular Recognition between β-Sheets

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Synthetic Procedures

Commercial-grade reagents and solvents were used without further purification. Flash column chromatography was performed with silica gel following the conditions described by Still and coworkers.¹

**Preparation of 2-BuO-C₆H₄-CO₂Et.**² A three-necked, round-bottomed flask equipped with a septum, a stopper, and a mechanical stirrer was charged with a solution of salicylic acid (5.00 g, 30.1 mmol) in 60 mL of DMF, 1-bromobutane (8.25 g, 60.2 mmol), and freshly ground K₂CO₃ powder (14.55 g, 105.3 mmol). This mixture was heated to 70 °C for 3 h and then poured into 200 mL of EtOAc and 200 mL of H₂O. The layers were separated, the aqueous layer was extracted with 200 mL of EtOAc, and this EtOAc extract was washed with 2 x 100 mL of aqueous 1 M NaOH and combined with the previous EtOAc extract. The combined EtOAc extracts were dried over MgSO₄, filtered, and concentrated under vacuum to a colorless oil, which was purified by column chromatography (1:15 EtOAc-hexane) to afford 5.16 g (77%) of colorless oil.²

**Preparation of 2-BuO-C₆H₄-CO₂H.**² A solution of 2-BuO-C₆H₄-CO₂Et (5.16 g, 23.2 mmol), 46 mL of dioxane, and 28 mL of aqueous 1.2 M NaOH was heated to reflux for 1 h. The solution was concentrated to ~10 mL and diluted to 110 mL with H₂O. This aqueous solution was washed with 2 x 50 mL of CH₂Cl₂, acidified with aqueous 1 M HCl, and extracted with 1 x 100 mL CH₂Cl₂ and 2 x 100 mL of EtOAc. The combined CH₂Cl₂ and EtOAc extracts were concentrated to a colorless oil under vacuum, which

was purified by column chromatography (1:10 EtOAc-hexane) to afford 4.03 g (89%) of a colorless oil.²

**Preparation of PS-Indole-NHMe resin.**

A solid-phase synthesis reaction vessel was charged with PS-NH₂•HCl resin (5.00 g, 1.10 mmol/g loading, 5.50 mmol) and DMF (100 mL), the resin was allowed to swell for 10 minutes, and the DMF was drained.³ To the reaction vessel, (3-formyl-1-indolyl)acetic acid (2.24 g, 11 mmol), 147 mL of CH₂Cl₂, 22 mL of DMF, HOBt (2.98 g, 22 mmol), diisopropylcarbodiimide (DIC) (2.78 g, 3.44 mL, 22 mmol), and DIPEA (1.44 mL, 8.25 mmol) were added, and the resin was shaken for 96 hours. The solution was drained and the resin was washed with 3 x 100 mL of CH₂Cl₂. The coupling with (3-formyl-1-indolyl)acetic acid was then repeated, as described above. After final wash with 3 x 100 mL of CH₂Cl₂, the resin was dried by purging with nitrogen overnight. 1,2-Dichloroethane (250 mL) was added to the vessel and resin allowed to swell for 10 minutes. A 6 M solution of MeNH₂ in THF (20 mL, 120 mmol) and Me₄NBH(OAc)₃ (7.24 g, 27.5 mmol) were added to the reaction vessel and it was shaken for 48 hours. Sodium cyanoborohydride (8.64 g, 138 mmol) was then added to the reaction vessel along with 45 mL of methanol, and the vessel was shaken for another 24 hours. The resin

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was then washed with 3 x 100 mL of CH$_3$OH, 3 x 100 mL of CH$_2$Cl$_2$, and 3 x 100 mL of Et$_2$O and dried by purging with N$_2$. The loading of the resin was assayed after the derivatization by coupling of Fmoc-Ala-OH to a small portion of the resin (ca. 10 mg), deprotecting Fmoc with 20% piperidine, and measuring optical density at 290 nm.$^4$

Typical loading: 0.45 mmol/g.

**Preparation of peptides.$^5$** Solid-phase reactions were performed in parallel, six to eight at once, on a Quest™ 210 parallel synthesizer, using Fmoc-protected amino acids and were monitored by the Kaiser test.$^6$ Each solid-phase reaction vessel was charged with PS-indole-NHMe resin (0.11 g, 0.45 mmol/g, 0.050 mmol) and a solution of amino acid (0.20 mmol), HOBt (0.20 mmol), DIPEA (0.20 mmol), HBTU (0.20 mmol), and 2 mL of DMF-CH$_2$Cl$_2$ (1:1). The reaction mixture was agitated for 0.5-1 h and a small sample of resin was checked by the Kaiser test. Then, the solution was drained and the resin was washed with 3 x 5 mL of DMF, 3 x 5 mL of CH$_3$OH, and 3 x 5 mL of CH$_2$Cl$_2$. Two (2) mL of 20% piperidine in DMF was added, the mixture was agitated for 10 min, the solution was drained, and the resin was washed with 3 x 5 mL of DMF, 3 x 5 mL of CH$_3$OH, and 3 x 5 mL of CH$_2$Cl$_2$. This procedure was repeated for all amino acids, except for Fmoc-Orn(i-Pr-CO-Hao)-OH.$^5$ Fmoc-Orn(i-Pr-CO-Hao)-OH was coupled by adding a solution of Fmoc-Orn(i-Pr-CO-Hao)-OH (0.20 mmol), HOAt (0.20 mmol), DIC (0.20 mmol), and 2 mL of DMF into the reaction vessel. The reaction mixture was agitated for 2 h, the solution was drained, and the resin was washed with 3 x 5 mL of DMF, 3 x 5 mL

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$^4$ NovaBiochem Catalog, 1999; p S43.


of CH$_3$OH, and 3 x 5 mL of CH$_2$Cl$_2$. Then, 2 mL of 20% piperidine in DMF was added to the resin, the mixture was agitated for 10 minutes, the solution was drained, and the resin was washed with 3 x 5 mL of DMF, 3 x 5 mL of CH$_3$OH, and 3 x 5 mL of CH$_2$Cl$_2$.

After all amino acids were coupled, 2-BuO-C$_6$H$_4$-CO$_2$H was coupled by adding a solution of 2-BuO-C$_6$H$_4$-CO$_2$H (0.20 mmol), HOAt (0.20 mmol), DIC (0.20 mmol), and 2 mL of 1:1 DMF-CH$_2$Cl$_2$ to the reaction vessel. The reaction mixture was agitated for 2 h. The solution was drained and the resin was washed with 3 x 5 mL of DMF, 3 x 5 mL of CH$_3$OH, and 3 x 5 mL of CH$_2$Cl$_2$. Then, 2 mL of 20% piperidine in DMF was added to the resin, the mixture was agitated for 10 minutes, the solution was drained, and the resin was washed with 3 x 5 mL of DMF, 3 x 5 mL of CH$_3$OH, and 3 x 5 mL of CH$_2$Cl$_2$. After 2-BuO-C$_6$H$_4$-CO$_2$H was coupled, 3 mL of 2.5:2.5:95 of TIPS-H$_2$O-TFA cleavage cocktail was added, and the reaction mixture was agitated for 45-60 min. The solution was collected. Then, 2 mL of TFA was added and collected. The combined solution was concentrated under vacuum to a thin film of oil.

The crude product was redissolved in 10 mL of CHCl$_3$, and the solution was washed with 1 x 10 mL of saturated aqueous NaHCO$_3$, 2 x 10 mL of H$_2$O, dried over MgSO$_4$, and concentrated to a thin film of oil, which was purified by column chromatography (elution with 30 mL of 10:10:80 hexanes-EtOAc-CHCl$_3$ followed by 5:45:50 ethanol-CHCl$_3$-EtOAc) to afford 10-25 mg of peptide.

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7 The thin film of oil can be converted to a powder by rotary evaporation with MeOH.
NMR Studies

L-Peptides (1a-1d) were characterized by 1D 500 MHz $^1$H NMR spectroscopy and by 2D 500 MHz gCOSY, TOCSY, and Tr-ROESY experiments. D-Peptides (2a-2c) were characterized by 1D 500 MHz $^1$H NMR spectroscopy. An 800 MHz EXSY spectrum was acquired on a mixture of 1a and 2a. Mixtures of peptides (1a & 2a, 1b & 2b, 1c & 2c, 1d & 2c, 1a & 1b, and 1c & 1d) were studied by 1D 500 MHz $^1$H NMR spectroscopy. All NMR spectra were recorded and processed on a Bruker 500 MHz NMR spectrometer at 499.93 MHz with Bruker XWIN-NMR software, except for the 800 MHz EXSY spectrum. The EXSY spectrum was acquired on a Varian 800 MHz spectrometer with Varian software. Both spectrometers were tuned before data acquisition. All solutions were prepared using a fresh bottle of CDCl$_3$ containing 0.05% of v/v TMS which was used as a reference (0.00 ppm). $^1$H NMR resonances were numbered 1, 2, 3... starting with the most downfield resonance. These resonances were assigned to the corresponding protons in the peptides on the basis of the TOCSY, gCOSY, and Tr-ROESY data. Key cross-peaks in Tr-ROESY spectra were labeled with corresponding peak number. COSY Artifacts in the Tr-ROESY spectra were labeled with the word “COSY”. The following chart summarizes the important NOEs typically observed in the Tr-ROESY studies.

**Sample Preparation.** NMR samples were prepared by dissolving weighed samples of peptides 1 and 2 in appropriate volume of CDCl₃ to make 2.0 or 10 mM solutions. One dimensional (1D) studies were performed at 2.0 mM. Two dimensional (2D) studies were performed at 10 mM. Mixed studies were performed at 2.0 mM of each component. Solutions for the mixed studies were prepared by combining a 100-μL portion of a 10-mM solution of each of the two components with 300 μL of CDCl₃. Solutions were not degassed.

**Data Acquisition.** One- and two- dimensional spectra of peptides 1 and 2 were acquired at 298 K. One dimensional spectra of peptides mixture were collected at 253 K. The 800 MHz EXSY spectrum of a mixture of 1a and 2a was collected at 308 K. gCOSY, TOCSY, and Tr-ROESY spectra were acquired with 2048 data points in the $f_2$ domain and 256 data points in the $f_1$ domain. TOCSY spectra were acquired with a 150-ms spin-
lock mixing time and Tr-ROESY spectra were acquired with a 250-ms spin-lock mixing
time. The 800 MHz EXSY was acquired using a standard NOESY pulse sequence and a
500-ms mixing time with 4096 points in the \( f_2 \) domain and 512 points in the \( f_1 \) domain at
308 K.

**Data Processing.** gCOSY, TOCSY, and Tr-ROESY spectra were processed by zero-
filling in the \( f_1 \) domain to yield a final matrix of 1024 by 1024 real points. Weighting
functions were applied as indicated on the individual spectrum (processing parameter
WDW). Automatic baseline correction was applied in both dimensions after the Fourier
transform. The EXSY spectrum was processed by zero filling in the \( f_1 \) domain to yield a
final matrix of 4096 by 2048 real points. Then, the data was Fourier transformed with a
sine squared bell weighting function with a 90° phase shift and automatic baseline
corrected in both dimensions. The homo- and heterodimer content of the mixture of
peptides was analyzed by fitting Lorentzian lines to the anilide NH resonances using the
ldcon command of the Bruker XWIN-NMR software.
L-Leu-Leu 1a
L-Leu-Leu 1a
L-Leu-Leu 1a
L-Leu-Leu 1a

29, 29', 29''
L-Leu-Leu 1a

ppm  0.0  1.4  1.5  1.6  1.7  1.8  1.9  2.0  2.1
Integral 0.999 2.084 1.056 11.866 1.386

31  32,32'  33  34,34'  35,35'  36  37  38
l-Leu-Leu 1a

GCOSY

Current Data Parameters

USER            mchung
NAME         DMCVIII-08
EXPNO                12
PROCNO                1

F2 - Acquisition Parameters
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Time               2.45
INSTRUM           gn500
PROBHD    5 mm broadban
PULPROG          cosygp
TD                 2048
SOLVENT          CDCl3T
NS                    2
DS                   16
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AQ            0.1278452 sec
RG                  362
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TE                300.0 K
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D1           1.00000000 sec
D13          0.00000300 sec
D16          0.00025000 sec
IN0          0.00012480 sec

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P1                11.75 usec
PL1               -3.00 dB
SFO1        499.9334995 MHz

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GPZ2              17.00 %
P16             1000.00 usec

F1 - Acquisition parameters
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LB                 0.00 Hz
GB                    0
PC                 4.00

2D NMR plot parameters
CX2               15.00 cm
CX1               15.00 cm
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F2LO            6005.94 Hz
F2PHI            -0.211 ppm
F2HI            -105.40 Hz
F1PLO            12.014 ppm
F1LO            6005.94 Hz
F1PHI            -0.211 ppm
F1HI            -105.40 Hz
F2PPMCM         0.81496 ppm/cm
F2HZCM        407.42273 Hz/cm
F1PPMCM         0.81496 ppm/cm
F1HZCM        407.42273 Hz/cm
L-Leu-Leu 1a
GCOSY
L-Leu-Leu 1a
GCOSY
L-Leu-Leu 1a
GCOSY
L-Leu-Leu 1a
GCOSY
**L-Leu-Leu 1a**

**TOCSY**

---

**2D NMR plot parameters**
- CX2: 15.00 cm
- CX1: 15.00 cm
- F2PLO: 12.014 ppm
- F2LO: 6005.94 Hz
- F2PHI: -0.211 ppm
- F2HI: -105.40 Hz
- F1PLO: 12.014 ppm
- F1LO: 6005.94 Hz
- F1PHI: -0.211 ppm
- F1HI: -105.40 Hz
- F2PPMCM: 0.81496 ppm/cm
- F2HZCM: 407.42273 Hz/cm
- F1PPMCM: 0.81496 ppm/cm
- F1HZCM: 407.42273 Hz/cm

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**TOCSY**

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ROESY
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COSY

15,16

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D-Val-Ala 2c

ppm

Integral

ppm

S117
EXSY Spectrum for L-Leu-Leu mixed with D-Leu-Leu
EXSY Spectrum for L-Leu-Leu mixed with D-Leu-Leu

- Homochiral anilide NH resonance
- Heterochiral anilide NH resonance
- Heterochiral hydrazide NH resonance 1
- Homochiral hydrazide NH resonance 1
- Heterochiral hydrazide NH resonance 2
- Homochiral hydrazide NH resonance
Mixture of L-Leu-Leu 1a and D-Leu-Leu 2a
Mixture of L-Leu-Leu 1a and D-Leu-Leu 2a
Deconvolution of NH resonances of mixture of l-Leu-Leu 1a and D-Leu-Leu 2a as Lorentzian lines with Bruker XWIN-NMR software Idcon command

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Mixture of L-Val-Val 1b and D-Val-Val 2b
Mixture of L-Val-Val 1b and D-Val-Val 2b

- Homochiral dimer hydrazide NH signal
- Homochiral dimer anilide NH signal
- Heterochiral dimer
- D-Val-Val 2b
- Homochiral dimer anilide NH signal
- L-Val-Val 1b
- Homochiral dimer anilide NH signal
Deconvolution of NH resonances of mixture of L-Val-Val \textbf{1b} and D-Val-Val \textbf{2b} as Lorentzian lines with Bruker XWIN-NMR software Idcon command

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S126
Mixture of L-Val-Ala 1c and D-Val-Ala 2c
Mixture of D-Val-Ala 2c and L-Val-Ala 1c
Deconvolution of NH resonances of mixture of L-Val-Ala 1c and D-Val-Ala 2c as Lorentzian lines with Bruker XWIN-NMR software Idcon command

Data set: /v/data/mchung/nmr/DMCVIII-044/13/pdata/1

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Mixture of L-Ala-Val 1d and D-Val-Ala 2c
Mixture of L-Ala-Val 1d and D-Val-Ala 2c

homochiral dimer hydrazide NH signal

heterochiral dimer

homochiral dimer anilide NH signal

D-Val-Ala 2c

homochiral dimer anilide NH signal

L-Ala-Val 1d

homochiral dimer anilide NH signal
Deconvolution of NH resonances of mixture of L-Ala-Val 1d and D-Val-Ala 2c as Lorentzian lines with Bruker XWIN-NMR software Idcon command

Data set: /v/data/mchung/nmr/DMCVIII-044/14/pdata/1

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Mixture of L-Leu-Leu 1a and L-Val-Val 1b
Mixture of L-Leu-Leu 1a and L-Val-Val 1b

L-Val-Val homodimer 1b-1b hydrazide NH signals
L-Val-Val homodimer 1b-1b anilide NH signals
L-Leu-Leu homodimer 1a-1a hydrazide NH signals
L-Leu-Leu homodimer 1a-1a anilide NH signals
Deconvolution of NH resonances of mixture of l-Leu-Leu $1^a$ and l-Val-Val $1^b$ as Lorentzian lines with Bruker XWIN-NMR software Idcon command

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S135
Mixture of L-Val-Ala 1c and L-Ala-Val 1d
Mixture of L-Val-Ala 1c and L-Ala-Val 1d

- L-Ala-Val homodimer 1d-1d hydrazide NH signals
- L-Val-Ala homodimer 1c-1c hydrazide NH signals
- L-Ala-Val homodimer 1d-1d anilide NH signals
- L-Val-Ala homodimer 1c-1c anilide NH signals
Deconvolution of NH resonances of mixture of L-Val-Ala 1c and L-Ala-Val 1d as Lorentzian lines with Bruker XWIN-NMR software ldcon command

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2.6e+11

4.2e+11
Molecular Model of Homochiral Dimer 1c•1c

Reasonable model of a local minimum energy conformation generated using MacroModel V6.5 with the AMBER* force field and GB/SA CHCl₃ solvation.
Molecular Model of Heterochiral Dimer 1c•2c

Reasonable model of a local minimum energy conformation generated using MacroModel V6.5 with the AMBER* force field and GB/SA CHCl₃ solvation.