Structural Studies of β-Turn-Containing Peptide Catalysts for Atroposelective Quinazolinone Bromination

Anthony J. Metrano,[†] Nadia C. Abascal,[†]

Brandon Q. Mercado, Eric K. Paulson, and Scott J. Miller*

Department of Chemistry, Yale University, New Haven, CT 06520-8107, United States

*E-mail: scott.miller@yale.edu

[†] A.J.M. and N.C.A. contributed equally.

Electronic Supplementary Information

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I. General Information

Room temperature (rt) is defined as 21–23 °C. All reagents were purchased from commercial suppliers and used without further purification, unless otherwise noted. In particular, *N*-bromosuccinimide (NBS) was recrystallized from water, dried thoroughly *in vacuo*, and stored in a vial shielded from light at 0 ºC. Methylene chloride (CH_2Cl_2), and toluene (PhMe) were obtained from a Seca Solvent System by GlassContour, in which the solvent was dried over alumina and dispensed under an atmosphere of Ar. All other solvents were purchased from commercial suppliers and used without further purification.

Routine ^{1}H-NMR spectra were recorded on Agilent 500 MHz spectrometers at ambient temperature. NMR solvents, *d*-chloroform, d_6-dimethylsulfoxide, d_6-benzene, and d_4-methanol were purchased from Cambridge Isotope Laboratories and used without further purification. *d*-Chloroform was stored at ambient temperature over 4 Å molecular sieves, and fresh d_4-methanol and d_6-benzene ampules were used immediately after opening. Spectra were processed with MestReNova 10.0.2 using the automatic phasing and Bernstein third order polynomial baseline correction capabilities. Splitting was determined using the automatic multiplet analysis function with intervention as necessary. Spectral data are reported as follows: chemical shift (multiplicity [singlet (s), doublet (d), triplet (t), quartet (q), pentet (p), multiplet (m), doublet of doublets (dd), doublet of doublet of doublets (ddd), doublet of triplet of doublets (dtd), doublet of triplets (dt), triplet of doublets (td), etc.], coupling constant, integration). Chemical shifts are reported in ppm (δ), and coupling constants are reported in Hz. ^{1}H-Resonances are referenced to solvent residual peaks for $CDCl_3$ (7.26 ppm), DMSO-d_6 (2.50 ppm), C_6D_6 (7.16 ppm), or CD_3OD (3.31 ppm).[1] Routine ^{13}C-NMR spectra were recorded on Agilent 500 MHz spectrometers with protons fully decoupled. ^{13}C-Resonances are reported in ppm relative to solvent residual peaks for $CDCl_3$ (77.2 ppm), DMSO-d_6 (39.5 ppm), C_6D_6 (128.1 ppm), or CD_3OD (49.0 ppm).[1]

Infrared spectra were recorded on a Nicolet 6700 ATR/FT-IR spectrometer, and ν_{max} are partially reported in cm^{-1}. Samples for high-resolution liquid chromatography-mass spectrometry (HRMS) were submitted to the Mass Spectrometry Laboratory at the University of Illinois at Urbana-Champaign. Data was acquired on a Waters Synapt G2-Si instrument equipped with an ESI detector. For crude analysis, ultra high-performance liquid chromatography-mass spectrometry (UPLC/MS) was performed on a Waters Acquity UPLC/MS instrument equipped with a reverse-phase BEH C18 column (1.7 µm particle size, 2.1 x 50 mm), a dual atmospheric pressure chemical ionization (API)/electrospray ionization (ESI) mass spectrometry detector, and a photodiode array detector.

Analytical thin-layer chromatography (TLC) was performed using 60 Å Silica Gel F_{254} pre-coated plates (0.25 mm thickness). TLC plates were visualized by irradiation with a UV lamp. R_f values are reported. Normal-phase flash chromatography was performed using a Biotage Isolera One purification system equipped with a 10, 25, or 50 g SNAP Ultra (HP Sphere, 25 mm silica) cartridge and an appropriate EtOAc/hexanes linear gradient in the mobile phase. Reverse-phase column chromatography was performed using a Biotage Isolera One purification

system equipped with a 60 or 120 g SNAP-C18 column and an appropriate MeOH/H_2O linear gradient in the mobile phase.

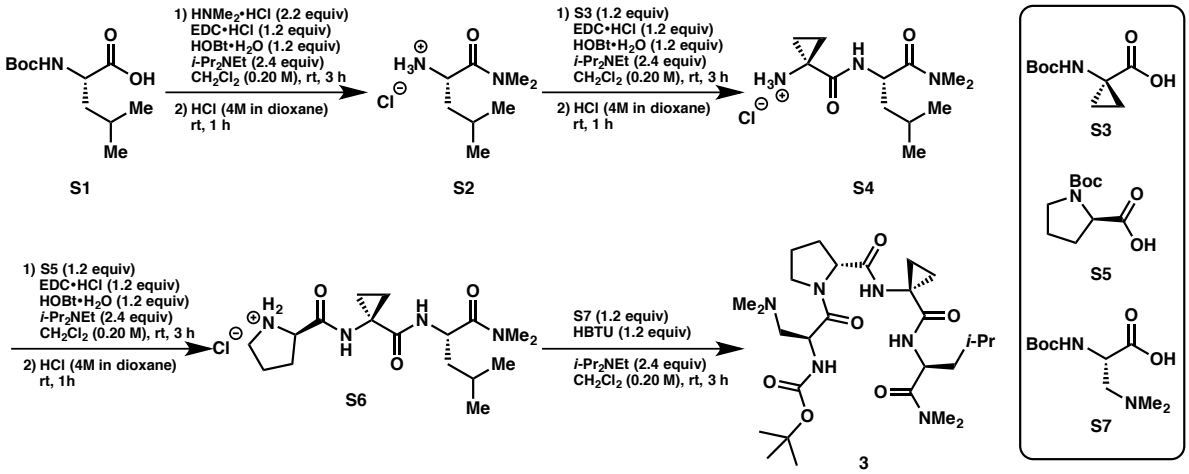
Optical rotations were recorded on a Perkin-Elmer Polarimeter 341 at the sodium D-line (589 nm) using a cell of 1 dm path length. Measurements were recorded at 20 ºC. Concentration values are reported in units of g/100 mL. Normal-phase high-performance liquid chromatography (HPLC) was performed using an Agilent 1100 series instrument equipped with a diode array detector and columns (chiral supports) from Daicel Chemical Industries (Chiralcel OJ-H).

II. Solution Phase Peptide Synthesis and Characterization

A. General Remarks

The solution phase peptide synthesis of catalysts **3**, **4a–x**, and **S11–18** was accomplished using the *N-tert*-butoxycarbonyl (Boc) protecting group strategy.[2] Boc-L-β-Dimethylaminoalanine (**S7**, Boc-Dmaa-OH) was synthesized according to a literature procedure.[3] All other amino acid residues and coupling reagents were purchased from commercial suppliers. Once synthesized, peptides were stored at 0 °C to prevent epimerization and other adverse side-reactivity.

B. Synthesis and Characterization of Dimethylamide-Containing Peptide 3



Installation of *C*-Terminal Protecting Group: Boc-Leu-OH•H_2O (**S1**, 499 mg, 2.00 mmol), dimethylamine hydrochloride (359 mg, 4.40 mmol), and HOBt•H_2O (368 mg, 2.40 mmol) were added to a round bottom flask equipped with a magnetic stir bar. The solid mixture was dissolved in CH_2Cl_2 (10 mL, 0.20 M w.r.t. **S1**), and EDC•HCl (460 mg, 2.40 mmol) was added. The resulting solution was allowed to stir at rt as *i*-Pr_2NEt (0.84 mL, 4.80 mmol) was added slowly, causing the cloudy solution to clarify. The pale yellow reaction solution was allowed to stir at rt for about 2 h, after which the solution was poured into a separatory funnel, diluted to 30 mL with additional CH_2Cl_2, and washed with approximately 25 mL of 10% aqueous (w/v) citric acid. The organic layer was separated and subsequently washed with 25 mL each of saturated aqueous $NaHCO_3$ and brine. The organics were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to provide a clear, pale yellow oil (517 mg, > 99% crude yield). The identity of Boc-Leu-NMe_2 was confirmed by UPLC/MS. **MS:** Exact mass calculated for $[C_{13}H_{26}N_2O_3 + H]^+$ requires *m/z* = 259.2. Found 259.2 (ESI+).

Deprotection 1: Crude Boc-Leu-NMe_2 was then treated with 6 mL of 4.0 M HCl in 1,4-dioxane to cleave the Boc group. The resulting pale yellow solution was allowed to stir at rt for 1 h before HCl and 1,4-dioxane were removed *in vacuo*. Residual 1,4-dioxane was removed by co-

evaporation with CH_2Cl_2 to provide 389 mg (> 99% crude yield) of **S2** as a foam, which was dried thoroughly under reduced pressure before being carried forward to the next coupling step.

Peptide Coupling 1: To a flask containing H-Leu-NMe_2•HCl (**S2**, 389 mg, 2.00 mmol) was added Boc-Acpc-OH (**S3**, 483 mg, 2.20 mmol), HOBt•H_2O (368 mg, 2.40 mmol), and a magnetic stir bar. The solid mixture was dissolved in dry CH_2Cl_2 (10.0 mL, 0.20 M w.r.t. **S2**), and EDC•HCl (460 mg, 2.40 mmol) was then added. The resulting solution was allowed to stir at rt as *i*-Pr_2NEt (0.84 mL, 4.80 mmol) was added slowly. The deep yellow reaction solution was allowed to stir at rt for 2 h, after which the solution was poured into a separatory funnel, diluted to 30 mL with additional CH_2Cl_2, and washed with 25 mL of 10% aqueous (w/v) citric acid. The organic layer was separated and subsequently washed with 25 mL each of saturated aqueous $NaHCO_3$ and brine. The organics were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to provide a white foam (739 mg, > 99% crude yield). The identity of Boc-Acpc-Leu-NMe_2 was confirmed by UPLC-MS. **MS:** Exact mass calculated for $[C_{17}H_{31}N_3O_4 + H]^+$ requires *m/z* = 342.2. Found 342.3 (ESI+).

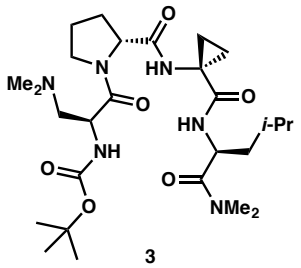
Deprotection 2: Deprotection of the crude dipeptide Boc-Acpc-Leu-NMe_2 was accomplished in the same manner as described in Deprotection 1 (*vide supra*) to provide **S4** (556 mg, 2.00 mmol) as a white foam.

Peptide Coupling 2: To a flask containing H-Acpc-Leu-NMe_2•HCl (**S4**, 556 mg, 2.00 mmol) was added Boc-D-Pro-OH (**S3**, 517 mg, 2.20 mmol), HOBt•H_2O (368 mg, 2.40 mmol), and a magnetic stir bar. The solid mixture was dissolved in dry CH_2Cl_2 (10.0 mL, 0.20 M w.r.t. **S4**), and EDC•HCl (460 mg, 2.40 mmol) was then added. The resulting solution was allowed to stir at rt as *i*-Pr_2NEt (0.84 mL, 4.80 mmol) was added slowly. The deep yellow reaction solution was allowed to stir at rt for 2 h, after which the solution was poured into a separatory funnel, diluted to 30 mL with additional CH_2Cl_2, and washed with 25 mL of 10% aqueous (w/v) citric acid. The organic layer was separated and subsequently washed with 25 mL each of saturated aqueous $NaHCO_3$ and brine. The organics were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to provide a white foam (873 mg, > 99% crude yield). The identity of Boc-D-Pro-Acpc-Leu-NMe_2 was confirmed by UPLC-MS. **MS:** Exact mass calculated for $[C_{22}H_{38}N_4O_5 + H]^+$ requires *m/z* = 439.3. Found 439.4 (ESI+).

Deprotection 3: Deprotection of the crude tripeptide Boc-D-Pro-Acpc-Leu-NMe_2 was accomplished in the same manner as described in Deprotection 1 (*vide supra*) to provide **S6** (750 mg, 2.00 mmol) as an off-white foam.

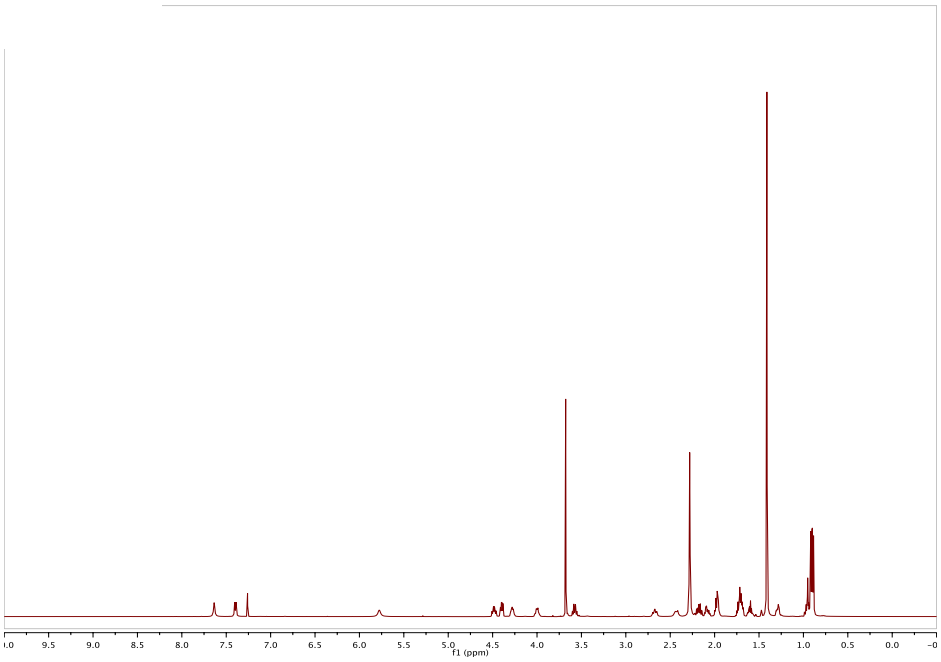
Peptide Coupling 3: To a flask containing H-D-Pro-Acpc-Leu-NMe_2•HCl (**S6**, 750 mg, 2.00 mmol) was added Boc-Dmaa-OH (**S7**, 511 mg, 2.20 mmol) and a magnetic stir bar. The solid mixture was dissolved in CH_2Cl_2 (10.0 mL, 0.20 M w.r.t. **S6**), and HBTU (910 mg, 2.40 mmol) was then added to the stirring solution at rt. Next, *i*-Pr_2NEt (0.84 mL, 4.80 mmol) was added slowly. The deep yellow/brown reaction solution was allowed to stir at rt for 8 h, after which the solution was poured into a separatory funnel, diluted to 30 mL with additional CH_2Cl_2, and washed twice with about 25 mL of saturated aqueous $NaHCO_3$. The organic layer was

separated and subsequently washed with 20 mL of brine. The organics were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to provide a deep yellow oil. The crude product was loaded onto a Biotage Isolera One purification system for reverse-phase column chromatography (120 g column, 30-100% MeOH/H_2O over 16 column volumes with 3 column volume pre- and post-run equilibrations, 45 mLmin^{-1} flow, collection λ = 210 nm, monitored λ = 254 nm, 16 x 150 mm test tubes with 20 mL fractions). Fractions were pooled, concentrated *in vacuo*, and dried thrice azeotropically with CH_2Cl_2 to provide Boc-Dmaa-D-Pro-Acpc-Leu-NMe_2 (**3**, 667 mg, 60% yield) as a white foam.



3

Boc-Dmaa-D-Pro-Acpc-Leu-NMe_2 (3): White foamy solid, 60% overall yield from **S1**. **IR** (FT-ATR, cm^{-1}): 3301, 2969, 2873, 1627, 1519, 1445, 1245, 1165, 1010. **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 7.55 (d, *J* = 8.5 Hz, 1H), 7.16 (s, 1H), 6.48 (d, *J* = 6.3 Hz, 1H), 4.92 (td, *J* = 8.6, 5.1 Hz, 1H), 4.39 (q, *J* = 7.1 Hz, 1H), 4.36 (dd, *J* = 7.6, 4.1 Hz, 1H), 4.03–3.91 (m, 1H), 3.60 (dt, *J* = 9.9, 6.8 Hz, 1H), 3.10 (s, 3H), 2.91 (s, 3H), 2.72 (dd, *J* = 12.3, 7.6 Hz, 1H), 2.46 (dd, *J* = 12.3, 7.2 Hz, 1 H), 2.26 (s, 6H), 2.16–2.10 (m, 3H), 1.99–1.90 (m, 1H), 1.73–1.61 (m, 2H), 1.55–1.46 (m, 3H), 1.40 (s, 9H), 0.97 (dq, *J* = 6.3, 3.2 Hz, 2H), 0.92 (dd, *J* = 9.4, 6.4 Hz, 6H). **^{13}C-NMR** (125 MHz, $CDCl_3$): δ 172.5, 172.3, 171.5, 171.1, 156.5, 79.9, 76.9, 61.3, 60.1, 50.6, 47.7, 47.5, 45.9, 41.8, 37.3, 36.0, 34.6, 28.9, 28.5, 25.1, 24.7, 23.4, 22.4, 17.2, 17.1. **HRMS:** Exact mass calculated for $[C_{27}H_{48}N_6O_6 + H]^+$ requires *m/z* = 553.3714. Found 553.3709 (ESI+). **Optical:** $[\alpha]_D^{20}$ = +40.2 (*c* = 1.0, CH_2Cl_2).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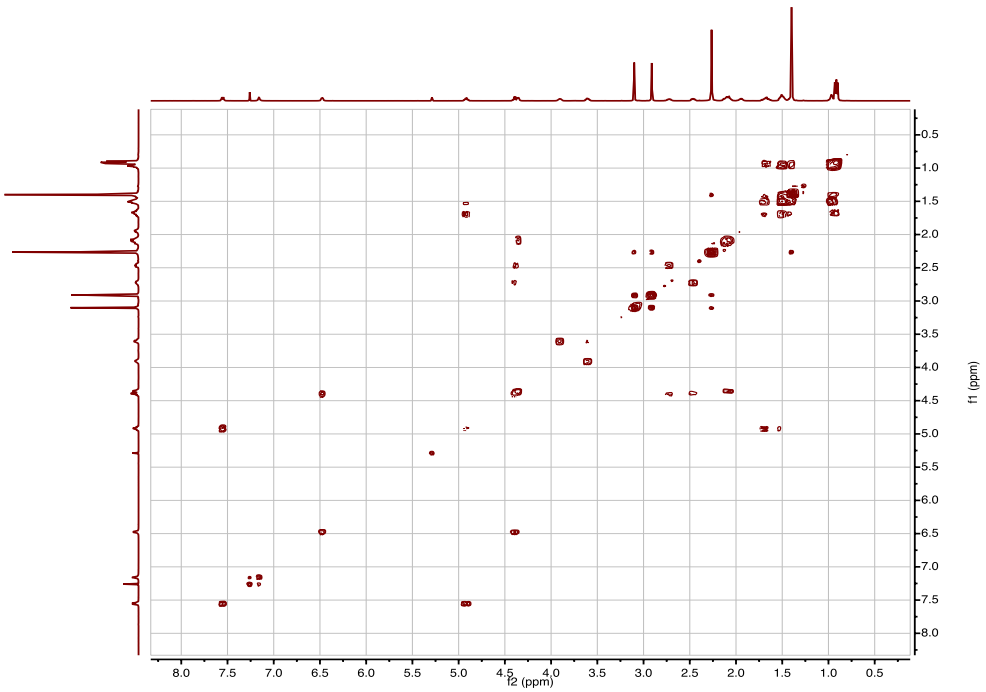
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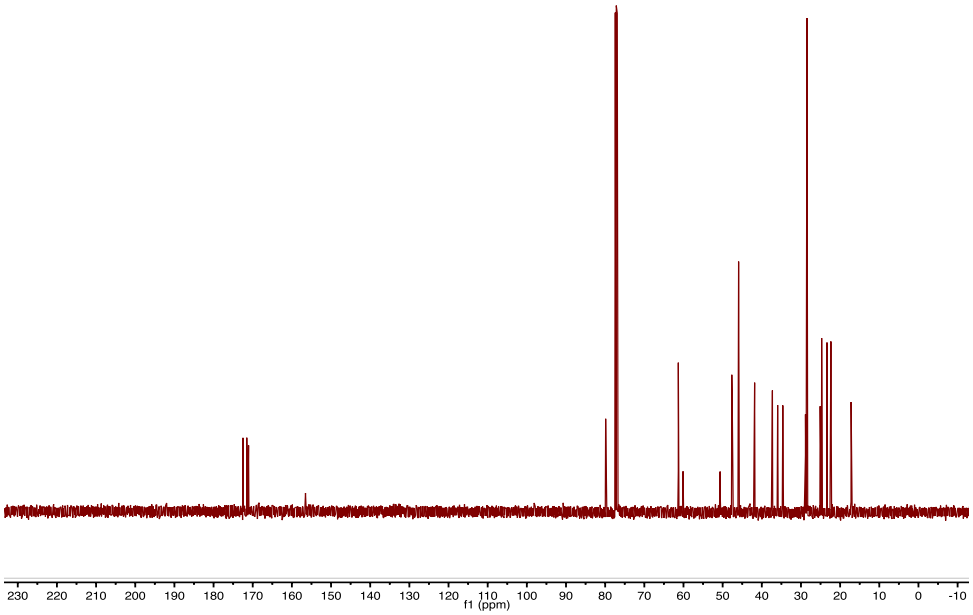
f1 (ppm)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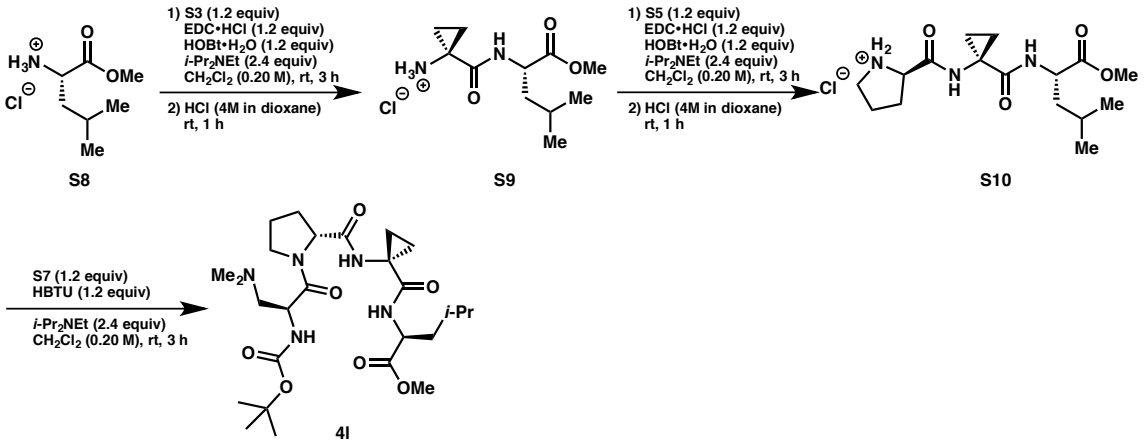
f1 (ppm)

C. Synthesis and Characterization of Methyl Ester-Containing Peptide 4l



Peptide Coupling 1: To a flask containing H-Leu-OMe•HCl (**S8**, 362 mg, 2.00 mmol) was added Boc-Acpc-OH (**S3**, 483 mg, 2.40 mmol), HOBt•H_2O (368 mg, 2.40 mmol), and a magnetic stir bar. The solid mixture was dissolved in dry CH_2Cl_2 (10.0 mL, 0.20 M w.r.t. **S8**), and EDC•HCl (460 mg, 2.40 mmol) was then added. The resulting solution was allowed to stir at rt as *i*-Pr_2NEt (0.84 mL, 4.80 mmol) was added slowly. The clear, colorless reaction solution was allowed to stir at rt for overnight, after which the solution was poured into a separatory funnel, diluted to 30 mL with additional CH_2Cl_2, and washed with 25 mL of 10% aqueous (w/v) citric acid. The organic layer was separated and subsequently washed with 25 mL each of saturated aqueous $NaHCO_3$ and brine. The organics were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to provide an off-white waxy solid (772 mg, > 99% crude yield). The identity of Boc-Acpc-Leu-OMe was confirmed by UPLC-MS. **MS:** Exact mass calculated for $[C_{16}H_{28}N_2O_5 + H]^+$ requires *m/z* = 329.2. Found 329.3 (ESI+).

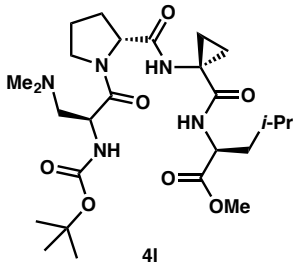
Deprotection 1: Crude Boc-Acpc-Leu-OMe was then treated with 6 mL of 4.0 M HCl in 1,4-dioxane to cleave the Boc group. The resulting pale yellow solution was allowed to stir at rt for 1 h, before HCl and 1,4-dioxane were removed *in vacuo*. Residual 1,4-dioxane was removed by co-evaporation with CH_2Cl_2 to provide 530 mg (> 99% crude yield) of **S9** as a foam, which was dried thoroughly under reduced pressure before being carried forward to the next coupling step.

Peptide Coupling 2: To a flask containing H-Acpc-Leu-OMe•HCl (**S9**, 530 mg, 2.00 mmol) was added Boc-D-Pro-OH (**S5**, 517 mg, 2.20 mmol), HOBt•H_2O (368 mg, 2.40 mmol), and a magnetic stir bar. The solid mixture was dissolved in dry CH_2Cl_2 (10.0 mL, 0.20 M w.r.t. **S9**), and EDC•HCl (460 mg, 2.40 mmol) was then added. The resulting solution was allowed to stir at rt as *i*-Pr_2NEt (0.84 mL, 4.80 mmol) was added slowly. The clear, pale yellow reaction solution was allowed to stir at rt for 3 h, after which the solution was poured into a separatory funnel, diluted to 30 mL with additional CH_2Cl_2, and washed with 25 mL of 10% aqueous (w/v) citric acid. The organic layer was separated and subsequently washed with 25 mL each of saturated aqueous $NaHCO_3$ and brine. The organics were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to provide a white foam (851 mg, 1.86 mmol, 93% crude yield). The

identity of Boc-D-Pro-Acpc-Leu-OMe was confirmed by UPLC-MS. **MS:** Exact mass calculated for $[C_{21}H_{35}N_3O_6 + H]^+$ requires *m/z* = 426.3. Found 426.4 (ESI+).

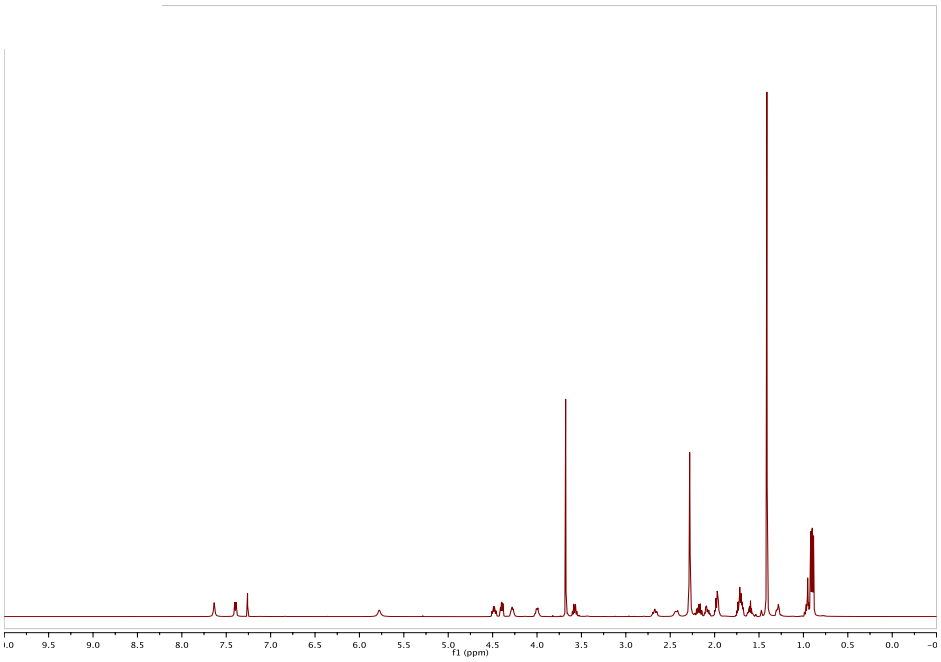
Deprotection 2: Deprotection of the crude tripeptide Boc-D-Pro-Acpc-Leu-OMe was accomplished in the same manner as described in Deprotection 1 (*vide supra*) to provide 672 mg of **S10** (1.86 mmol, > 99% crude yield) as an off-white foam.

Peptide Coupling 3: To a flask containing H-D-Pro-Acpc-Leu-OMe•HCl (**S10**, 672 mg, 1.86 mmol) was added Boc-Dmaa-OH (**S76**, 518 mg, 2.23 mmol) and a magnetic stir bar. The solid mixture was dissolved in CH_2Cl_2 (9.3 mL, 0.20 M w.r.t. **S10**), and HBTU (846 mg, 2.23 mmol) was then added to the stirring solution at rt. Next, *i*-Pr_2NEt (0.78 mL, 4.46 mmol) was added slowly. The deep yellow reaction solution was allowed to stir at rt for 8 h, after which the solution was poured into a separatory funnel, diluted to 30 mL with additional CH_2Cl_2, and washed twice with about 25 mL of saturated aqueous $NaHCO_3$. The organic layer was separated and subsequently washed with 20 mL of brine. The organics were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to provide a deep yellow oil. The crude product was loaded onto a Biotage Isolera One purification system for reverse-phase column chromatography (120 g column, 30-100% MeOH/H_2O over 16 column volumes with 3 column volume pre- and post-run equilibrations, 45 $mLmin^{-1}$ flow, collection λ = 210 nm, monitored λ = 254 nm, 16 x 150 mm test tubes with 20 mL fractions). Fractions were pooled, concentrated *in vacuo*, and dried thrice azeotropically with CH_2Cl_2 to provide Boc-Dmaa-D-Pro-Acpc-Leu-OMe (**4l**, 759 mg, 76% yield) as a white foam.



4l

Boc-Dmaa-D-Pro-Acpc-Leu-OMe (**4l**)**:** White foamy solid, 76% overall yield from **S8**. **IR** (FT-ATR, cm^{-1}): 3322, 2956, 1744, 1669, 1644, 1539, 1506, 1442, 1367, 1254, 1169, 1023. **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.64 (s, 1H), 7.40 (d, *J* = 7.7 Hz, 1H), 5.78 (s, 1H), 4.48 (ddd, *J* = 9.0, 7.6, 5.3 Hz, 1H), 4.40 (dd, *J* = 8.5, 4.3 Hz, 1H), 4.34–4.22 (m, 1H), 4.00 (dt, *J* = 9.9, 6.3 Hz, 1H), 3.68 (s, 3H), 3.58 (dt, *J* = 9.7, 7.5 Hz, 1H), 2.67 (t, *J* = 11.1 Hz, 1H), 2.48–2.35 (m, 1H), 2.28 (s, 6H), 2.18 (dq, *J* = 12.9, 8.2 Hz, 1H), 2.13–2.02 (m, 1H), 2.02–1.89 (m, 2H), 1.71 (ddt, *J* = 13.8, 6.7, 5.0 Hz, 3H), 1.60 (tt, *J* = 9.9, 5.3 Hz, 1H), 1.41 (s, 9H), 1.31–1.27 (m, 1H), 1.02 - 0.93 (m, 1H), 0.90 (dd, *J* = 9.6, 6.2 Hz, 6H). **^{13}C-NMR** (125 MHz, $CDCl_3$): δ 173.5, 172.3, 171.5, 171.2, 156.7, 80.7, 77.4, 77.2, 76.9, 61.7, 59.4, 51.9, 51.6, 50.8, 47.9, 45.7, 41.3, 34.6, 29.5, 28.5, 28.4, 24.8, 24.8, 23.0, 22.0, 17.1, 16.8. **HRMS:** Exact mass calculated for $[C_{26}H_{45}N_5O_7 + H]^+$ requires *m/z* = 540.3397. Found 540.3394 (ESI+). **Optical:** $[\alpha]_D^{20}$ = –2.96 (*c* = 1.0, $CHCl_3$).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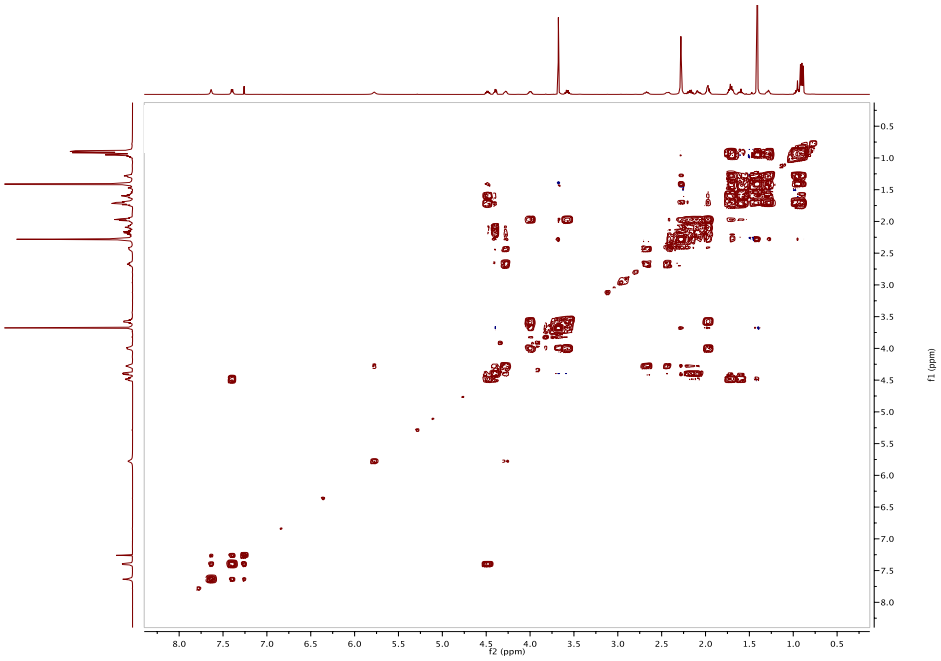
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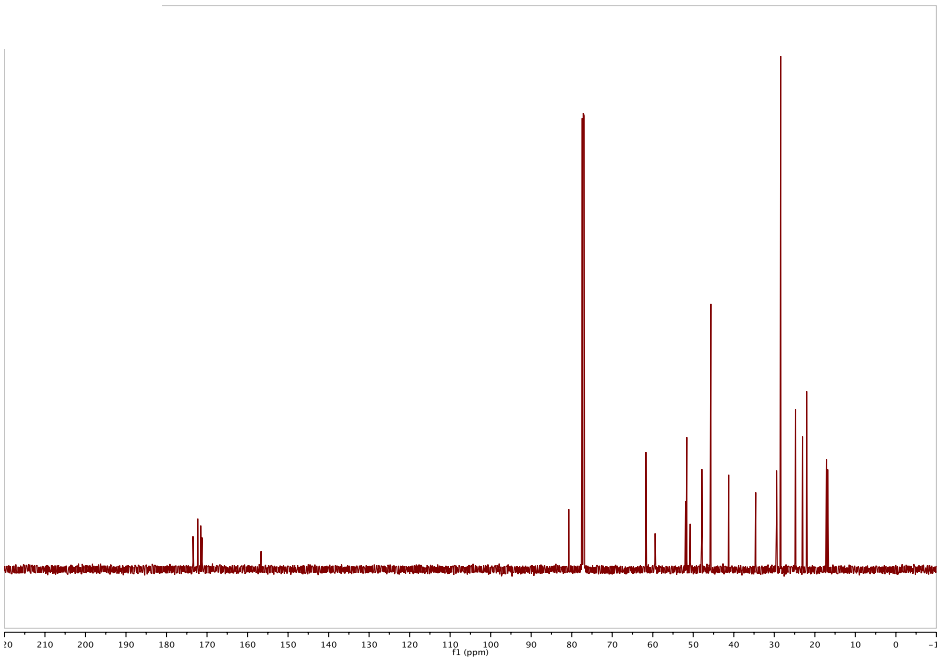
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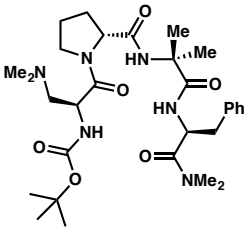
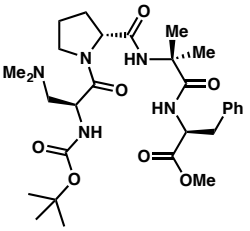
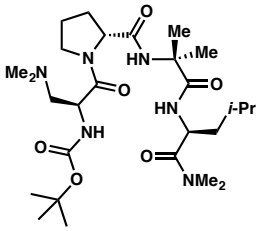
D. HRMS Data for Peptide Catalysts 4a–k, 4m–x, and S11–18



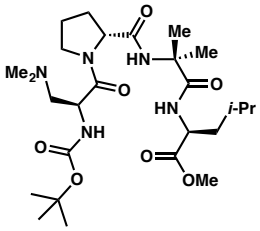
4a
Calculated $[C_{30}H_{48}N_6O_6 + H]^+$
requires *m/z* = 589.3714.
Found 589.3707.



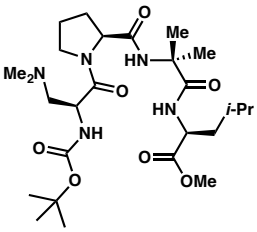
4b
Calculated $[C_{29}H_{45}N_5O_7 + H]^+$
requires *m/z* = 576.3397.
Found 576.3389.



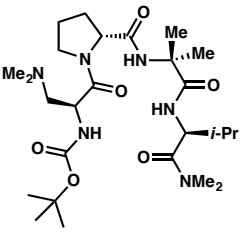
4c
Calculated $[C_{27}H_{50}N_6O_6 + H]^+$
requires *m/z* =555.3870.
Found 555.3869.



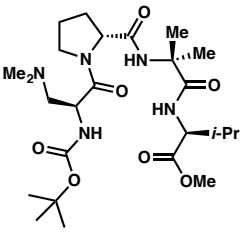
4d
Calculated $[C_{26}H_{47}N_5O_7 + H]^+$
requires *m/z* = 542.3554.
Found 542.3543.



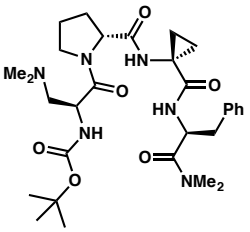
4e
Calculated $[C_{26}H_{47}N_5O_7 + H]^+$
requires *m/z* = 542.3554.
Found 542.3555.



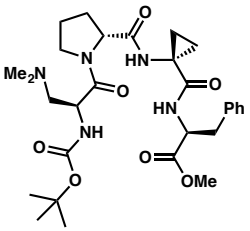
4f
Calculated $[C_{26}H_{48}N_6O_6 + H]^+$
requires *m/z* = 541.3714.
Found 541.3718.



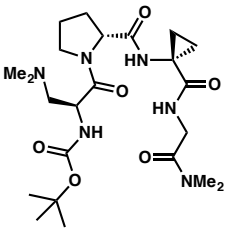
4g
Calculated $[C_{25}H_{45}N_5O_7 + H]^+$
requires *m/z* =528.3397.
Found 528.3398.



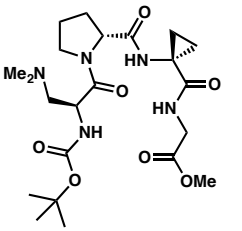
4h
Calculated $[C_{30}H_{46}N_6O_6 + H]^+$
requires *m/z* = 587.3557.
Found 587.3549.



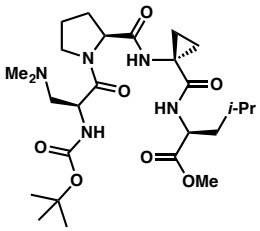
4i
Calculated $[C_{29}H_{43}N_5O_7 + H]^+$
requires *m/z* = 574.3241.
Found 574.3235.



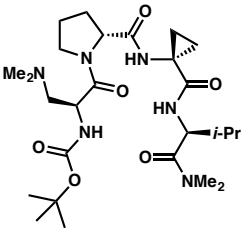
4j
Calculated $[C_{23}H_{40}N_6O_6 + H]^+$
requires *m/z* = 497.3088.
Found 497.3081.



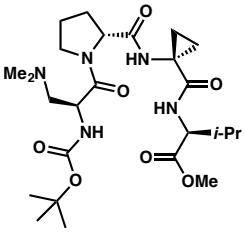
4k
Calculated $[C_{22}H_{37}N_5O_7 + H]^+$
requires *m/z* = 484.2771.
Found 484.2768.



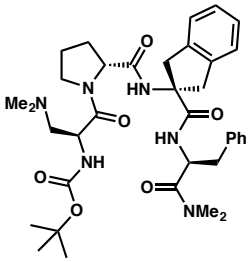
4m
Calculated $[C_{26}H_{45}N_5O_7 + H]^+$
requires *m/z* = 540.3397.
Found 540.3387.



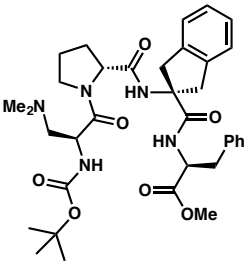
4n
Calculated $[C_{26}H_{46}N_6O_6 + H]^+$
requires *m/z* = 539.3557.
Found 539.3555.



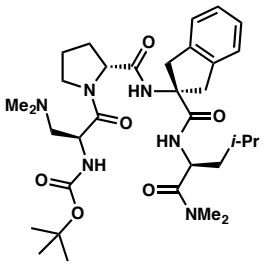
4o
Calculated $[C_{25}H_{43}N_5O_7 + H]^+$
requires *m/z* = 526.3241.
Found 526.3240.



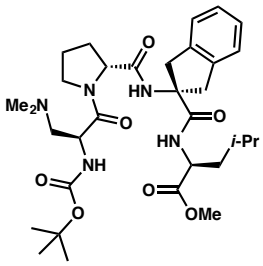
4p
Calculated $[C_{36}H_{50}N_6O_6 + H]^+$
requires *m/z* = 663.3870.
Found 663.3863.



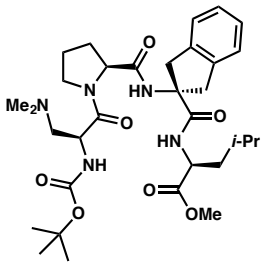
4q
Calculated $[C_{35}H_{47}N_5O_7 + H]^+$
requires *m/z* = 650.3554.
Found 650.3557.



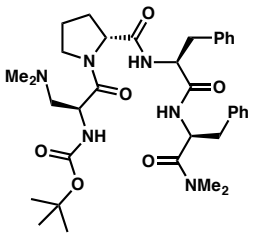
4r
Calculated $[C_{33}H_{52}N_6O_6 + H]^+$
requires *m/z* = 629.4027.
Found 629.4022.



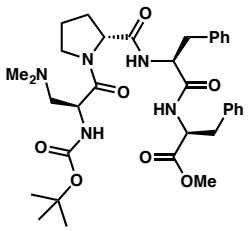
4s
Calculated $[C_{32}H_{49}N_5O_7 + H]^+$
requires *m/z* = 616.3710.
Found 616.3706.



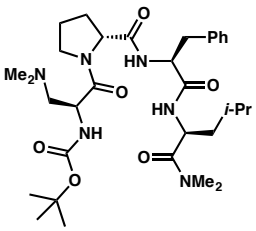
4t
Calculated $[C_{32}H_{49}N_5O_7 + H]^+$
requires *m/z* = 616.3710.
Found 616.3702.



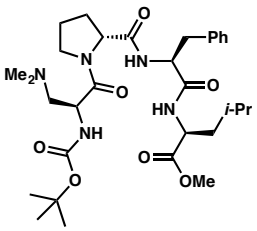
4u
Calculated $[C_{35}H_{50}N_6O_6 + H]^+$
requires *m/z* = 651.3870.
Found 651.3858.



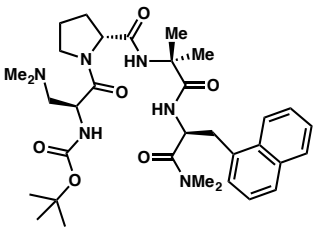
4v
Calculated $[C_{34}H_{47}N_5O_7 + H]^+$
requires *m/z* = 638.3554.
Found 638.3544.



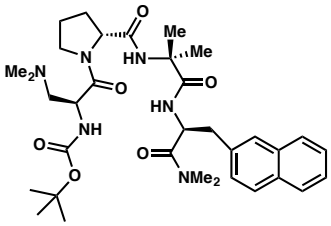
4w
Calculated $[C_{32}H_{52}N_6O_6 + H]^+$
requires *m/z* = 617.4027.
Found 617.4023.



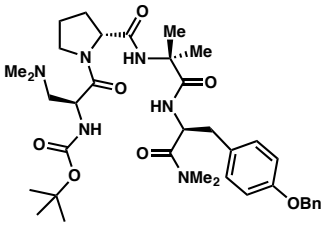
4x
Calculated $[C_{31}H_{49}N_5O_7 + H]^+$
requires *m/z* = 604.3710.
Found 604.3716.



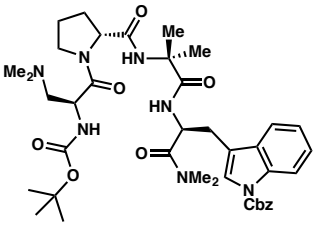
S11
Calculated $[C_{34}H_{50}N_6O_6 + H]^+$
requires *m/z* = 639.3870.
Found 639.3865.



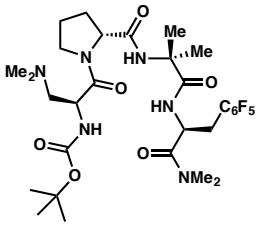
S12
Calculated $[C_{34}H_{50}N_6O_6 + H]^+$
requires *m/z* = 639.3870.
Found 639.3861.



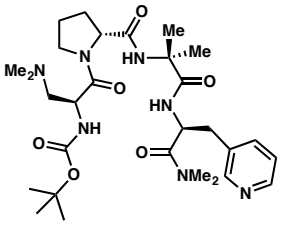
S13
Calculated $[C_{37}H_{54}N_6O_7 + H]^+$
requires *m/z* = 695.4132.
Found 695.4125.



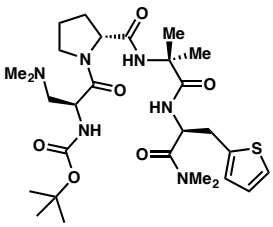
S14
Calculated $[C_{40}H_{55}N_7O_8 + H]^+$
requires *m/z* = 762.4190.
Found 762.4184.



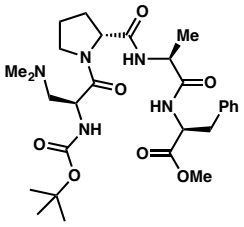
S15
Calculated $[C_{30}H_{43}F_5N_6O_6 + H]^+$
requires *m/z* = 679.3242.
Found 679.3240.



S16
Calculated $[C_{29}H_{47}N_7O_6 + H]^+$
requires *m/z* = 590.3666.
Found 590.3658.

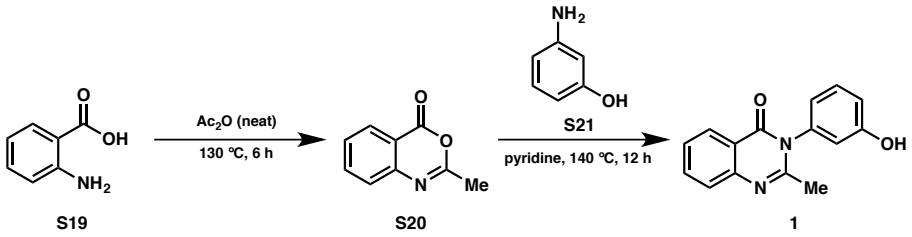


S17
Calculated $[C_{28}H_{46}N_6O_6S + H]^+$
requires *m/z* = 595.3278.
Found 595.3278.



S18
Calculated $[C_{28}H_{43}N_5O_7 + H]^+$
requires *m/z* = 562.3241.
Found 562.3237.

III. Synthesis and Characterization of Quinazolin-4(3*H*)-one 1

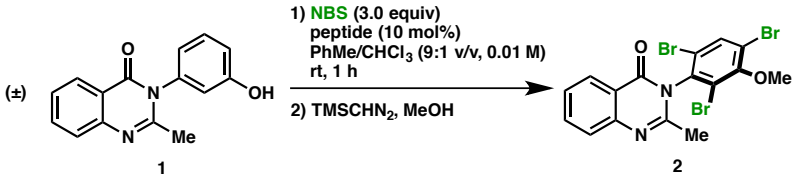


2-Methyl-4*H*-benzo-[*d*][1,3]oxazin-4-one (S20):[4] Anthranilic acid (**S19**, 8.228 g, 60.0 mmol) was added to an oven-dried 40 mL sealed tube (thick-walled) equipped with a magnetic stir bar. The off-white solid was suspended in acetic anhydride (36 mL, 381 mmol), and the vessel was purged with nitrogen, sealed tightly, and submerged into an oil bath at 130 ºC. The cloudy suspension quickly became a clear, deep yellow solution, which was allowed to stir at 130 °C for 6 h. The reaction solution was allowed to cool to room temperature, and the contents of the sealed tube were transferred to a round bottom flask washing with copious PhMe. Removal of solvent under reduced pressure yielded benzoxazinone **S20** (9.503 g, 98% yield) which was used without further purification.

3-(3-Hydroxyphenyl)-2-methylquinazolin-4(3*H*)-one (1):[5] Benzoxazinone **S20** (2.991 g, 18.6 mmol) and *m*-aminophenol (**S21**, 2.430 g, 22.3 mmol) were added to an oven-dried 40 mL sealed tube (thick-walled) equipped with a magnetic stir bar. The solid mixture was dissolved in pyridine (16.7 mL, 1.2 M w.r.t. **S20**). The vessel was purged with nitrogen, sealed tightly, and submerged in an oil bath at 145 °C. The cloudy, deep red suspension began to clarify upon heating. The deep red solution was allowed to stir for 12 h at 145 ºC, after which the vessel was cooled to room temperature. The contents of the sealed tube were transferred to a round bottom flask, washing with copious PhMe, and the solvent was removed under reduced pressure. The crude product was purified by automated flash chromatography using a gradient of 10–100% EtOAc/hexanes. Fractions were pooled and concentrated *in vacuo* to provide a pale yellow solid, which was suspended in hot CH_2Cl_2 and vacuum filtered to remove insoluble side-products. The filtrate was allowed to cool to 0 ºC, precipitating 2.563 g (61% yield) of pure **1** as a white solid. **TLC:** R_f = 0.21 (50% EtOAc/hexanes). **IR** (FT-ATR, cm^{-1}): 3310, 3090, 2819, 1661, 1591, 1570, 1291, 1112, 933. **^{1}H-NMR** (400 MHz, DMSO-d_6): δ 9.85 (s, 1H), 8.10 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.84 (ddd, *J* = 8.4, 7.1, 1.6 Hz, 1H), 7.66 (dd, *J* = 8.3, 1.1 Hz, 1H), 7.52 (ddd, *J* = 8.3, 7.2, 1.2 Hz, 1H), 7.36 (t, *J* = 8.0 Hz, 1H), 6.92 (ddd, *J* = 8.3, 2.4, 1.0 Hz, 1H), 6.84 (ddd, *J* = 7.8, 2.0, 0.9 Hz, 1H), 6.80 (t, *J* = 2.1 Hz, 1H), 2.17 (s, 3H). **^{13}C-NMR** (151 MHz, DMSO-d_6): δ 161.6, 158.7, 154.9, 147.7, 139.2, 134.9, 130.7, 127.1, 126.8, 126.7, 120.9, 119.2, 116.4, 115.8, 24.2. **HRMS:** Exact mass calculated for $[C_{15}H_{12}N_2O_2 + H]^+$ requires *m/z* = 253.0977. Found 253.0975 (ESI+).

IV. Bromination Procedures and Characterization of Tribromide 2

A. Peptide Screening Procedure



To an oven-dried 20 mL vial equipped with a magnetic stir bar was added 3-(3-hydroxyphenyl)-2-methyl-quinazolin-4(3*H*)-one (**1**, 12.6 mg, 0.050 mmol) and peptide catalyst (0.005 mmol, 10 mol% w.r.t. **1**). The solid mixture was suspended in 5 mL of PhMe/$CHCl_3$ (9:1 v/v, 0.01 M w.r.t. **1**), and the resulting suspension was allowed to stir vigorously at rt. *N*-Bromosuccinimide (NBS, 26.7 mg, 0.15 mmol, 3.0 equiv w.r.t. **1**) was added in one portion to the stirring solution at rt. The vial was sealed with a cap, and the reaction solution was allowed to stir for 60 minutes. (Note: A color change from colorless to yellow was observed within 15 minutes. In some cases, the clear yellow or pale yellow reaction solutions turned cloudy.) The reaction was quenched by addition of 1 mL of MeOH followed by (trimethylsilyl)diazomethane solution ($TMSCHN_2$, 2.0 M in hexanes) until the bright yellow color persisted in solution (Note: the yellow reaction solution became clear and colorless before turning bright yellow). The solution was allowed to stir 15–20 minutes at rt, after which glacial acetic acid was added dropwise until the solution became clear and colorless. The solvent was removed *in vacuo*, and the crude reaction mixture was purified by flash chromatography through a pipette silica plug (1 x 6 cm SiO_2) washing with EtOAc/hexanes (1:1 v/v). The fractions were pooled and concentrated *in vacuo*. The resulting white foam (or clear oil) was dried thoroughly on high vacuum to provide 3-(2,4,6-tribromo-3-methoxyphenyl)-2-methyl-quinazolin-4(3*H*)-one (**2**), which was analyzed by chiral HPLC to assess the enantioselectivity of the reaction. **Chiral HPLC** (Chiralcel OJ-H column, 10% EtOH/hexanes eluent, 2 mL injection, 1 $mLmin^{-1}$ flow rate, regulated at 20 °C, 230 nm)**:** major enantiomer t_R = 9.7 min, minor enantiomer t_R = 12.6 min. (Note: Conversion of **1** was always complete, and thus only er values were tabulated in Figure 2 and Figure S1.).

B. Cumulative Peptide Screening Data

Figure S1 presents our cumulative peptide results from this work, as well as our previous report.[6] All results were obtained using the Peptide Screening Procedure described above (section IV.A).

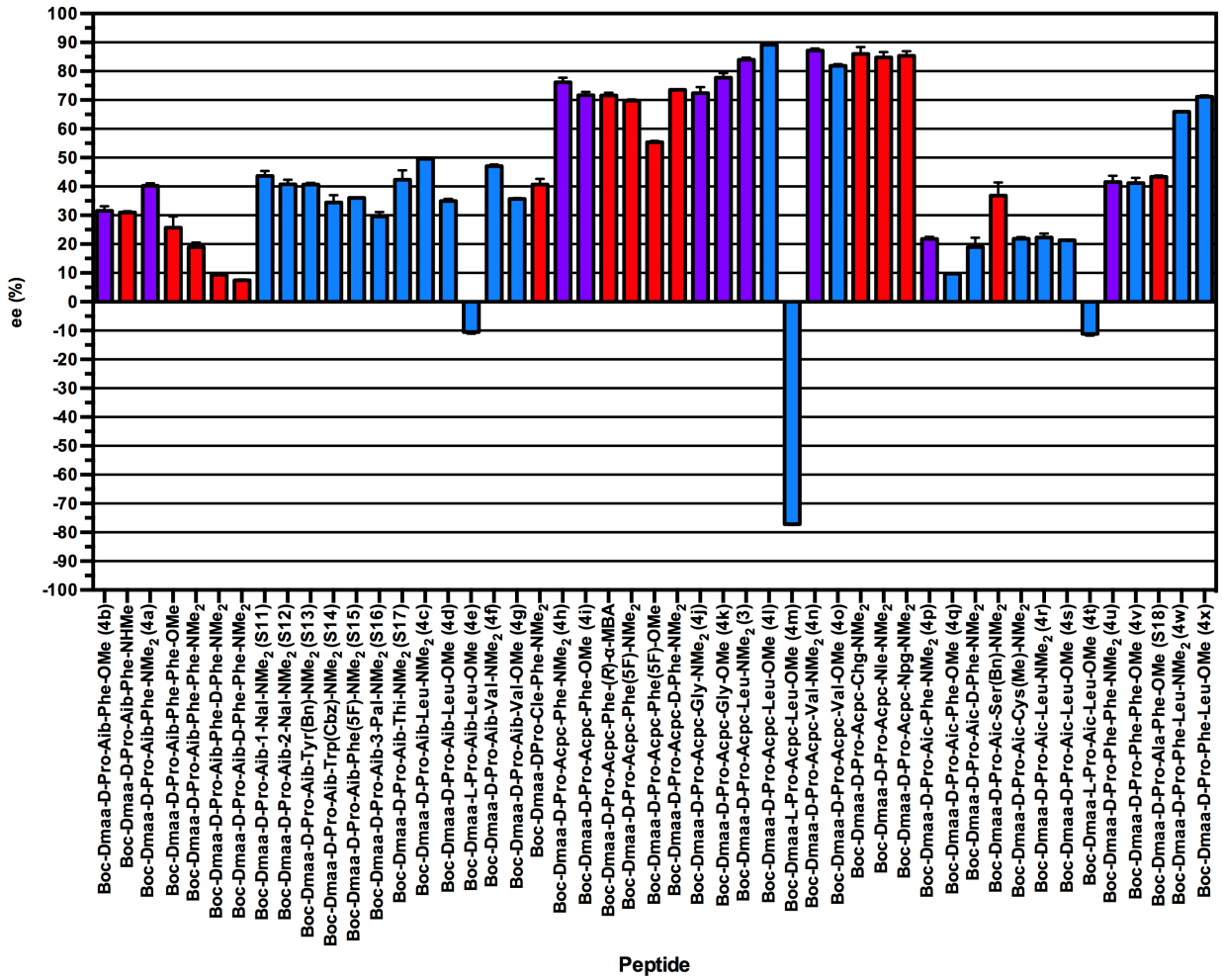
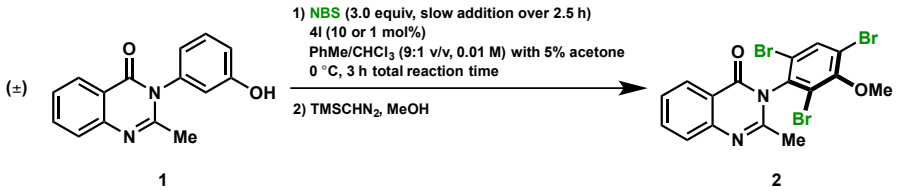


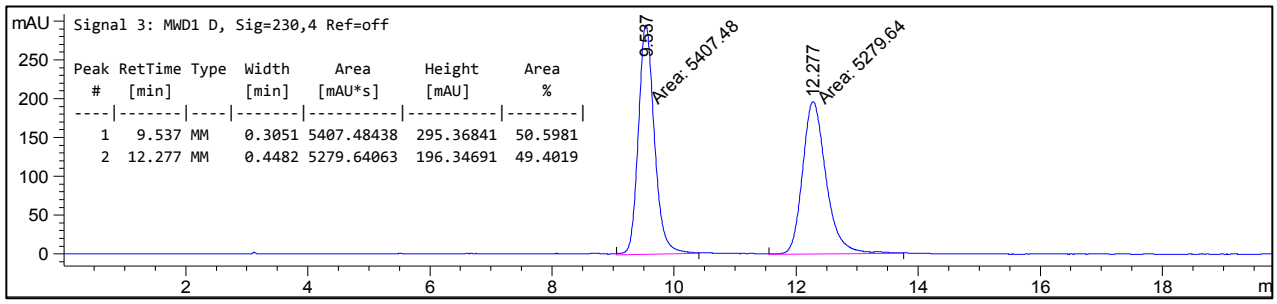
Figure S1: Cumulative peptide screening data for the atroposelective bromination of **1**. New entries from this study are presented in **blue**. Entries from ref. 6 are presented in **red**. Entries that appear in both ref. 6 and this study are in **purple**.

C. Preparative Bromination Procedure Using 4l

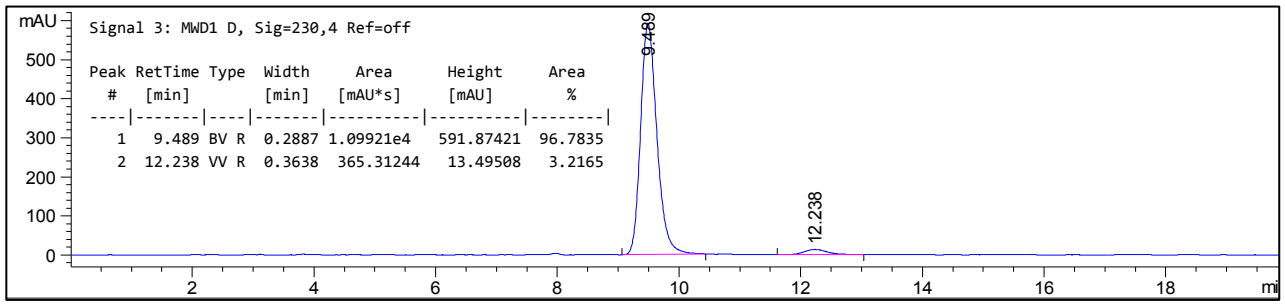


N-Bromosuccinimide (NBS, 53.3 mg, 0.30 mmol, 3.0 equiv w.r.t. **1**) was added to a 10 mL scintillation vial shielded from light, and 3.5 mL of PhMe/$CHCl_3$ (9:1 v/v) were added to the vial. The suspension of NBS was allowed to stir as 0.5 mL of acetone was added (to facilitate dissolution of NBS). The vial was sealed with a PTFE-lined cap, and the contents were allowed to stir at rt. Complete NBS dissolution typically required 5–10 minutes. In the meantime, quinazolinone **1** (25.2 mg, 0.10 mmol) and Boc-Dmaa-D-Pro-Acpc-Leu-OMe (**4l**, 5.4 mg, 0.01 mmol, 10 mol% w.r.t. **1** or 0.54 mg, 0.001 mmol, 1 mol% w.r.t. **1**) were added to a flame-dried 50 mL round bottom flask equipped with a magnetic stir bar. The solid mixture was suspended in 6 mL of PhMe/$CHCl_3$ (9:1 v/v), and the resulting cloudy suspension was allowed to stir vigorously under N_2 at 0 ºC. Once the NBS was *completely dissolved*, the delivery solution was taken up into a 5 mL syringe (12.46 mm diameter) and delivered into the substrate/peptide solution over 150 minutes (1.6 mLh^{-1}) at 0 °C using a syringe pump (Note: An 18 G needle was used to avoid clogging by NBS precipitation). During this time, the syringe was shielded from light using aluminum foil and the lights within the fume hood were turned off. After the addition was complete, the clear, colorless yellow solution was allowed to stir 30 minutes at under N_2. The reaction was quenched by addition of 2 mL of MeOH, followed by (trimethylsilyl)diazomethane solution ($TMSCHN_2$, 2 M in hexanes) until the bright yellow color persisted in solution. The solution was allowed to stir 15–20 minutes at rt, after which glacial acetic acid was added dropwise until the solution became clear and colorless. The solvent was removed *in vacuo*, and the crude reaction mixture was purified by flash chromatography on a Biotage Isolera One instrument (10 g SNAP Ultra column, 7–60% EtOAc/hexanes over 12 column volumes, loading in dichloromethane). The appropriate fractions were pooled, concentrated *in vacuo*, and dried thrice azeotropically with dichloromethane. The resulting white foam was dried thoroughly on high vacuum to provide 2-Methyl-3-(2,4,6-tribromo-3-methoxyphenyl)-quinazolin-4(3*H*)-one (**2**)[6] as a foamy, white solid in 92% yield when 10 mol% of **4l** was used and 80% yield when 1 mol% of **4l** was used. **TLC:** R_f = 0.32 (30% EtOAc/hexanes). **IR** (FT-ATR, cm^{-1}): 3067, 2937, 1690, 1605, 1569, 1371, 996. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 8.29 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.98 (s, 1H), 7.80 (ddd, *J* = 8.5, 7.1, 1.5 Hz, 1H), 7.71 (d, *J* = 8.1 Hz, 1H), 7.56 – 7.43 (m, 1H), 3.95 (s, 3H), 2.22 (s, 3H). **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 160.3, 155.4, 152.5, 147.5, 136.9, 135.9, 135.1, 127.3, 127.1, 126.9, 120.8, 120.4, 120.1, 118.8, 61.0, 22.9. **HRMS:** Exact mass calculated for $[C_{16}H_{11}N_2O_2Br_3 + H]^+$ requires *m/z* = 500.8448. Found 500.8449 (ESI+). **Optical:** $[\alpha]_D^{20}$ = +24.3 (*c* = 0.75, CH_2Cl_2, 97:3 er). **HPLC** (Chiralcel OJ-H column, 10% EtOH/hexanes eluent, 2 µL injection, 1 $mLmin^{-1}$ flow rate, regulated at 20 °C, 230 nm)**:** major enantiomer t_R = 9.5 min, minor enantiomer t_R = 12.4 min, 97:3 er (10 mol% **4l**) and 97:3 er (1 mol% **4l**).

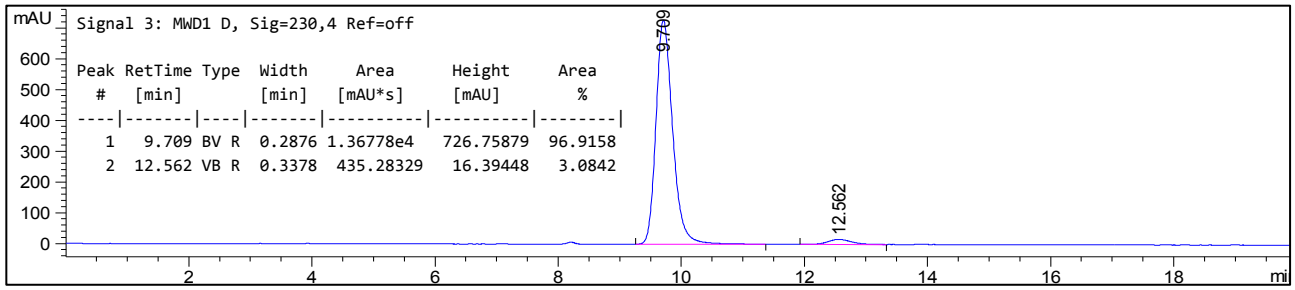
Racemic:



Enantioenriched using 10 mol% of 4l:



Enantioenriched using 1 mol% of 4l:



V. Solution-Phase NMR Studies of 3 and 4l

A. NMR Methods

To fully characterize peptides in solution, one-dimensional ^{1}H and two-dimensional gCOSY and NOESY experiments were carried out for each compound. All data were collected on Varian Inova 600 MHz spectrometers that were equipped with VnmrJ, version 4.2 revision A. Varian provided the pulse sequences for all experiments. All samples were prepared in C_6D_6 (with C_6H_6 set to 7.15 ppm)[1] at a concentration of 0.01 M, which was demonstrated to be below the aggregation limit for these peptides.

The NOESY spectra for **3** and **4l** were acquired at 25 °C and 20 ºC, respectively, the difference in temperatures being the result of instrument defaults at the time of acquisition. NOESY data for each peptide was collected with a mixing time of 300 ms, a spectral width of 9615.4 Hz, and a d1 time of 3 s. The data was acquired with a total of 256 transients, 1442 points in the f2 dimension, and 256 points in the f1 dimension. The spectra were processed using MestReNova, version 9.0.0-12821. Zero-filling sized the spectra to 2048, 2048. Automatic phasing was used in conjunction with manual adjustments. Additionally, apodization was accomplished with a sine square function (90º) in both dimensions. Each spectrum was automatically baseline corrected in each dimension using the Bernstein third order polynomial fit and treated with COSY-like symmetrization. The NOESY spectra of **3** and **4l** were inspected before and after symmetrization, and peaks deemed to be artifacts were discarded. Two peaks, both of which appeared in t1 ridges in the unsymmetrized data, were discarded from the analysis of peptide **4l**. Further refinement included treatment of the spectrum to reduce t1 noise.

NOESY spectra were integrated to extract distances from observed through-space interactions between protons on each peptide. After integrating NOESY cross-peaks, the peaks' volumes were converted to distances using the equation (ESI-1),[7] where r_{ij} is the calculated distance, r_{ref} is a reference distance, v_{ref} is the volume of a reference peak, and v_{ij} is the volume of the cross-peak in question. Reference peaks were chosen to be those that corresponded to interactions between δ-protons on the peptide's respective D-Pro residue. References distances that corresponded to these volumes were extracted from the appropriate peptide crystal structure.

$$r_{ij} = r_{ref} \sqrt[6]{\left(\frac{v_{ref}}{v_{ij}} \right)} \qquad \text{(ESI-1)}$$

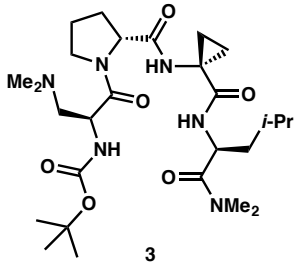
Integrated volumes were corrected using equation (ESI-2),[8] where v is the volume corresponding to either the reference or the peak in question from ESI-1, v_{raw} is the uncorrected volume of a peak in question, and v_{diag1} and v_{diag2} correspond to the volumes of the diagonal peaks for each respective interacting proton.

$$v = \frac{2v_{raw}}{\left(v_{diag1} + v_{diag2}\right)} \qquad \text{(ESI-2)}$$

The restraints were then processed using the standard *Crystallography and NMR Systems* (CNS)[9] simulated annealing protocol. A parameter file for each residue was assembled within the program. Each peptide was treated with the macro commands generate_seq, generate_extended, and anneal. By altering the energy-scoring threshold in the program's accept input file, we were able to cull the 10-lowest energy scored conformations for each structure. The accept feature of CNS also generated the average structure of these 10 conformers, which in turn, became the input for DFT calculations. Bins were defined at 1.8 to 2.5 Å, 1.8 to 3.0 Å, 1.8 to 3.5 Å, and 1.8 to 4.5 Å. Distances that were calculated to be over 4.5 Å were not included in the CNS restraint file.

The simulated annealing outputs from CNS were then used as a starting geometries for optimization and frequency calculation at the B3LYP/6-31G(d,p) level of theory using Gaussian 09.[10,11] Benzene was specified as the implicit solvent using the IEFPCM protocol.[12] Each structure was restrained using nOe-derived redundant internal coordinates. For peptide **3**, the following redundant internal coordinates were specified: NH_{Leu} to NH_{Dmaa} was restrained to 3.3 Å, β_{Dmaa} to β_{Leu} was restrained to 3.9 Å, and NH_{Leu} to $\alpha_{D\text{-}Pro}$ was restrained to 3.9 Å. For peptide **4l**, the following redundant internal coordinates were specified: NH_{Leu} to NH_{Dmaa} was restrained to 4.2 Å, NH_{Leu} to NH_{Acpc} was restrained to 3.2 Å, and NH_{Leu} to $\alpha_{D\text{-}Pro}$ was restrained to 3.7 Å. The optimization outputs were subsequently checked for consistency with the nOe-derived distances. In most cases, the optimized structures were in good accord with the NMR restraints.

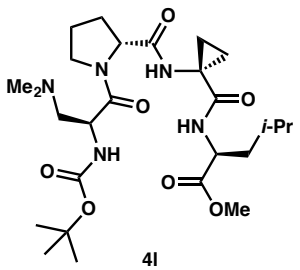
B. Full ^{1}H-NMR Assignment of Peptides 3 and 4l



3

^{1}H-NMR (600 MHz, 0.01 M in C_6D_6, 25 ºC)**:**[6] δ 8.06 (d, *J* = 8.7 Hz, 1H, NH_{Leu}), 7.10 (d, *J* = 7.2 Hz, 1H, NH_{Dmaa}), 6.74 (s, 1H, NH_{Acpc}), 5.25 (td, *J* = 9.2, 4.8 Hz, 1H, α_{Leu}), 4.56 (q, *J* = 7.4 Hz, 1H, α_{Dmaa}), 4.13 (dd, *J* = 8.7, 4.9 Hz, 1H, $\alpha_{D\text{-}Pro}$), 3.76 (dt, *J* = 9.8, 6.2 Hz, 1H, $\delta_{D\text{-}Pro}$), 3.22 (dt, *J* = 9.6, 7.1 Hz, 1H, $\delta'_{D\text{-}Pro}$), 2.87 (dd, *J* = 12.0, 6.0 Hz, 1H, β_{Dmaa}), 2.66 (s, 3H, N*Me*$_{Leu}$), 2.63 (s, 3H, N*Me*'$_{Leu}$), 2.54 (dd, *J* = 12.3, 6.4 Hz, 1H, β'_{Dmaa}), 2.12 (dd, *J* = 13.6, 4.8 Hz, 1H, β_{Leu}), 2.09 (s, 6H, 2x N*Me*$_{Dmaa}$), 2.04 (dtd, *J* = 8.4, 6.5, 4.9 Hz, 1H, γ_{Leu}), 1.93 – 1.87 (m, 1H, β_{Aic}), 1.78 (dt, *J* = 10.8, 3.8 Hz, 1H, β'_{Dmaa}), 1.72 (dt, *J* = 12.3, 6.1 Hz, 1H, $\beta_{D\text{-}Pro}$), 1.63 (ddd, *J* = 15.3, 7.6, 3.3 Hz, 1H, β'_{Leu}), 1.57 (dt, *J* = 14.4, 7.3 Hz, 1H, $\gamma_{D\text{-}Pro}$), 1.51 (s, 9H, *t*-Bu$_{Dmaa}$), 1.49 – 1.42 (m, 1H, $\beta'_{D\text{-}}$

$_{Pro}$), 1.19 (dt, *J* = 12.4, 6.3 Hz, 1H, $\gamma'_{D\text{-}Pro}$), 1.02 (dd, *J* = 9.2, 6.6 Hz, 6H, δ_{Leu}), 0.96 – 0.89 (m, 2H, β''_{Acpc}).



4l

^{1}H-NMR (600 MHz, 0.01 M in C_6D_6, 20 ºC)**:** δ 7.93 (d, *J* = 7.8 Hz, 1H, N*H*$_{Leu}$), 7.67 (s, 1H, N*H*$_{Acpc}$), 5.82 (s, 1H, N*H*$_{Dmaa}$), 5.06 (ddd, *J* = 10.0, 7.8, 4.6 Hz, 1H, α_{Leu}), 4.42 (dd, *J* = 8.7, 4.4 Hz, 1H, $\alpha_{D\text{-}Pro}$), 4.13 – 4.07 (m, 1H, α_{Dmaa}), 3.62 (td, *J* = 8.6, 5.0 Hz, 1H, $\delta_{D\text{-}Pro}$), 3.36 (s, 3H, O*Me*$_{Leu}$), 2.91 (q, *J* = 8.3 Hz, 1H, $\delta'_{D\text{-}Pro}$), 2.45 (dd, *J* = 12.2, 9.0 Hz, 1H, β_{Dmaa}), 2.28 – 2.22 (m, 1H, β_{Acpc}), 2.18 (m, 1H, γ_{Leu}), 2.16 (m, 1H, β_{Leu}), 2.11 (dd, *J* = 11.8, 5.8 Hz, 1H, β'_{Dmaa}), 1.82 (s, 6H, 2 x N*Me*$_{Dmaa}$), 1.80 (m, 1H, β'_{Leu}), 1.79 (m, 1H, $\beta_{D\text{-}Pro}$), 1.68 – 1.65 (m, 1H, β'_{Acpc}), 1.65 – 1.59 (m, 1H, $\beta'_{D\text{-}Pro}$), 1.53 (s, 9H, *t*-Bu$_{Dmaa}$), 1.46 – 1.38 (m, 1H, $\gamma_{D\text{-}Pro}$), 1.22 – 1.17 (m, 1H, β''_{Acpc}), 1.16 – 1.11 (m, 1H, $\gamma'_{D\text{-}Pro}$), 1.06 (ddd, *J* = 10.1, 7.6, 4.1 Hz, 1H, β'''_{Acpc}), 1.00 (dd, *J* = 30.0, 6.3 Hz, 6H, δ_{Leu}).

C. Tabular Representation of NOESY Cross-Peaks and Their Corresponding ^{1}H to ^{1}H Distances

The notation used below is as follows: each proton is designated by the three-letter code of its amino acid residue. Protons on the *tert*-butoxycarbonyl (Boc) *N*-terminal cap are called BocMe protons. Additional notation equates the following: A=α, B=β, C=γ, D=δ. Finally, for protons that are on the same carbon but are NMR-distinct, "1" is attributed to the more downfield proton and "2" to the more upfield proton. As an example, LeuHB1 is the notation for the more downfield β-proton of the leucine residue in our peptide. The NOESY spectrum and nOe-map for each peptide is shown below. Each nOe map is accompanied by a legend that color-codes the distance between the protons whose through-space interactions were detected by our NOESY experiments.

Peptide 3

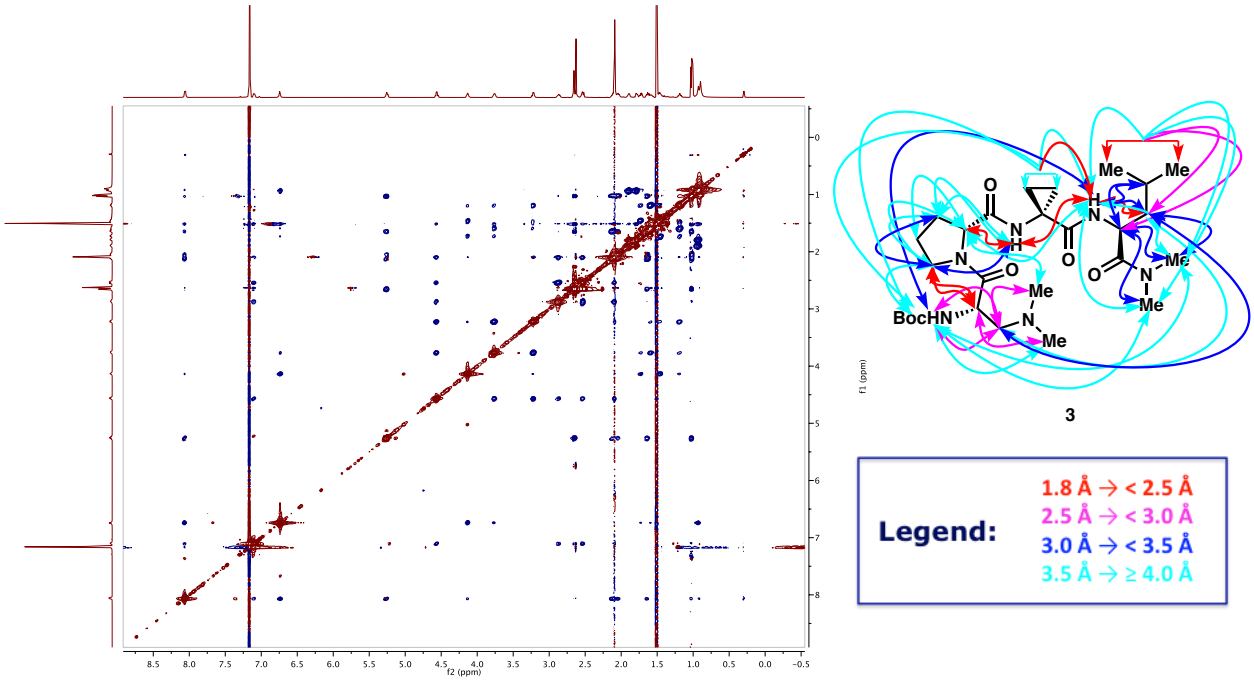


Table S1: NOESY-Derived Distances and Assignments for Peptide

	f2	f1	Normalized	Absolute	Assignment	Corrected Distances (Normalized)
1	8.06 1.02	1.04 8.06	-0.54 -0.64	-0.29 -0.34	LeuNH-LeuHD	4.29
2	8.06 0.91	0.92 8.07	-0.48 -0.52	-0.26 -0.28	LeuNH-AcpcHB1	3.66
3	8.06 7.11	7.11 8.08	-1 -0.97	-0.53 -0.52	LeuNH-DmaaNH	3.26
4	8.06 6.73	6.75 8.08	-5.67 -5.58	-3.02 -2.97	LeuNH-AcpcNH	2.42
5	8.06 2.03	2.04 8.06	-1.78 -1.7	-0.95 -0.91	LeuNH-LeuHC	3.00
6	8.06 2.11	2.11 8.06	-4.37 -4.59	-2.32 -2.44	LeuNH-LeuHB1	2.39
7	8.05 4.12	4.14 8.06	-0.4 -0.36	-0.21 -0.19	LeuNH-DProHA	3.89

8	8.05 1.64	1.65 8.07	-1.09 -1.04	-0.58 -0.56	LeuNH-LeuHB2	3.20
9	8.05 2.65	2.66 8.06	-0.1 -0.11	-0.05 -0.06	LeuNH-LeuNMe2	4.96
10	8.05 2.63	2.63 8.06	-0.08 -0.09	-0.04 -0.05	LeuNH-LeuNMe1	5.27
11	7.1 2.09	2.09 7.1	-0.81 -0.74	-0.43 -0.39	DmaaNH-DmaaMe	4.02
12	7.1 2.87	2.89 7.11	-2.51 -2.57	-1.33 -1.37	DmaaNH-DmaaHB2	2.78
13	7.1 2.66	2.66 7.1	-0.21 -0.17	-0.11 -0.09	DmaaNH-LeuNMe2	4.53
14	7.1 2.53	2.54 7.1	-2.56 -2.69	-1.36 -1.43	DmaaNH-DmaaHB1	2.80
15	7.1 2.63	2.63 7.1	-0.57 -0.56	-0.3 -0.3	DmaaNH-LeuNMe1	3.87
16	6.73 0.93	0.93 6.75	-5.4 -5.35	-2.87 -2.85	AcpcNH-AcpcHB1	2.48
17	6.73 3.76	3.77 6.74	-0.93 -0.94	-0.49 -0.5	AcpcNH-DProHD2	3.29
18	6.73 1.58	1.61 6.74	-0.44 -0.49	-0.23 -0.26	AcpcNH-DProHB1	3.68
19	6.73 1.72	1.73 6.74	-0.52 -0.44	-0.27 -0.23	AcpcNH-DProHB2	3.73
20	6.73 4.11	4.14 6.75	-7.81 -7.78	-4.16 -4.14	AcpcNH-DProHA	2.36
21	5.25 2.63	2.63 5.26	-2.6 -3.14	-1.38 -1.67	LeuHA-LeuNMe1	3.00
22	5.25 1.02	1.02 5.26	-8.02 -7.98	-4.27 -4.24	LeuHA-LeuHD	2.81
23	5.25 2.67	2.67 5.26	-8.26 -8.25	-4.39 -4.39	LeuHA-LeuNMe2	3.43
24	5.25 2.04	2.04 5.26	-2.02 -2.04	-1.07 -1.09	LeuHA-LeuHC	3.02
25	4.57 3.22	3.22 4.57	-9.7 -9.66	-5.16 -5.14	DmaaHA-DProHD1	2.26
26	4.56 3.76	3.76 4.57	-8.64 -8.65	-4.6 -4.6	DmaaHA-DProHD2	2.31
27	4.56 2.09	2.1 4.58	-7.21 -7.17	-3.83 -3.81	DmaaHA-DmaaMe	2.78
28	4.13 3.22	3.23 4.13	-0.52 -0.54	-0.28 -0.29	DProHA-DProHD1	3.70
29	4.13 1.19	1.2 4.14	-0.79 -0.85	-0.42 -0.45	DProHA-DProHC1	3.50
30	4.13 2.09	2.1 4.14	-0.25 -0.2	-0.13 -0.1	DProHA-DmaaMe	4.97
31	3.76 1.72	1.73 3.76	-1.12 -1.13	-0.6 -0.6	DProHD2-DProHB2	3.50
32	3.76 1.51	1.51 3.76	-0.73 -0.73	-0.39 -0.39	DProHD2-BocMe	4.30
33	3.22 1.46	1.46 3.22	-1.25 -1.25	-0.66 -0.66	DProHD1-DProHB1	3.18
34	2.88 1.64	1.64 2.87	-0.29 -0.33	-0.15 -0.17	DmaaHB2-LeuHB2	3.93
35	2.87 2.09	2.1 2.87	-8.64 -8.47	-4.59 -4.51	DmaaHB2-DmaaMe	2.68
36	2.66 1.64	1.63 2.66	-1.57 -1.47	-0.84 -0.78	LeuNMe2-LeuHB2	3.20
37	2.65 1.01	1.02 2.66	-1.31 -1.26	-0.69 -0.67	LeuNMe2-LeuHD	4.10
38	2.62 1.02	1.02 2.63	-0.43 -0.52	-0.23 -0.28	LeuNMe1-LeuHD	4.59
39	2.54 2.09	2.1 2.53	-7.49 -7.55	-3.98 -4.02	DmaaHB1-LeuHB2	2.93
40	1.64 1.02	1.02 1.64	-7.41 -7.67	-3.94 -4.08	LeuHB2-LeuHD	2.82
41	1.51	1.79	-1.53	-0.75	BocMe-AcpcHB	3.79

	1.79	1.51	-1.55	-0.76		
42	1.51 0.93	0.92 1.5	-1.13 -1.15	-0.56 -0.56	BocMe-AcpcHB	4.00
43	3.77 3.22	3.23 3.79	-35.57 -35.4	-18.91 -18.82	DProHD1-DProHD2	1.80

Peptide 4l

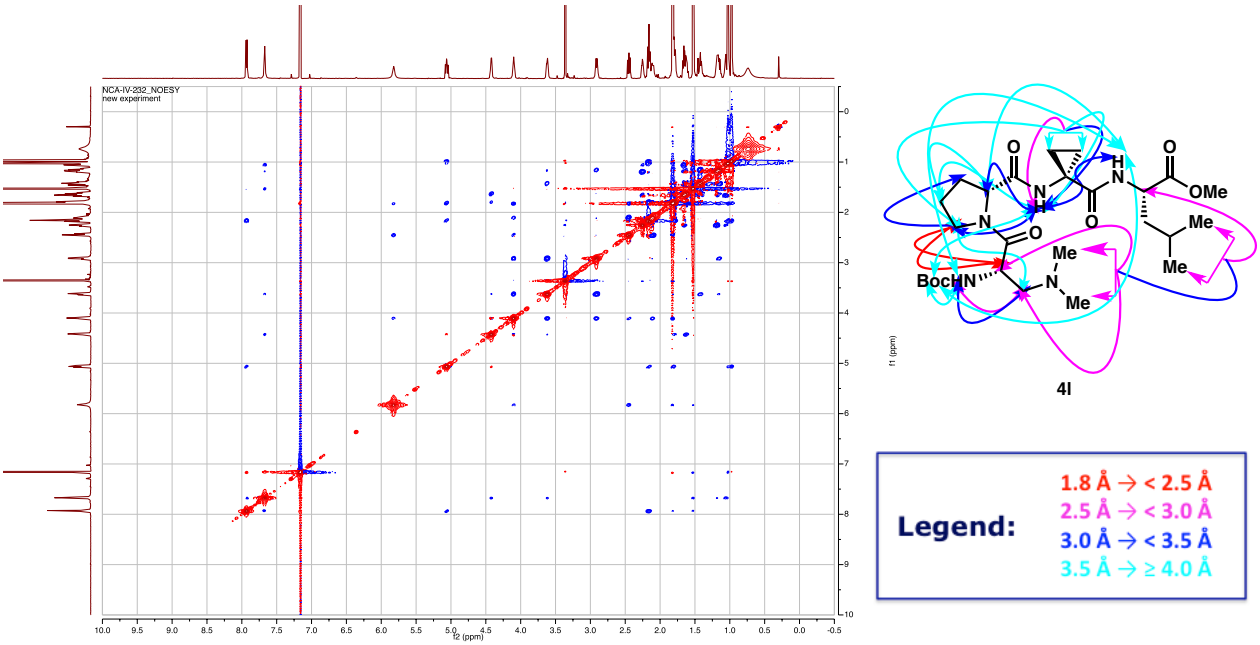
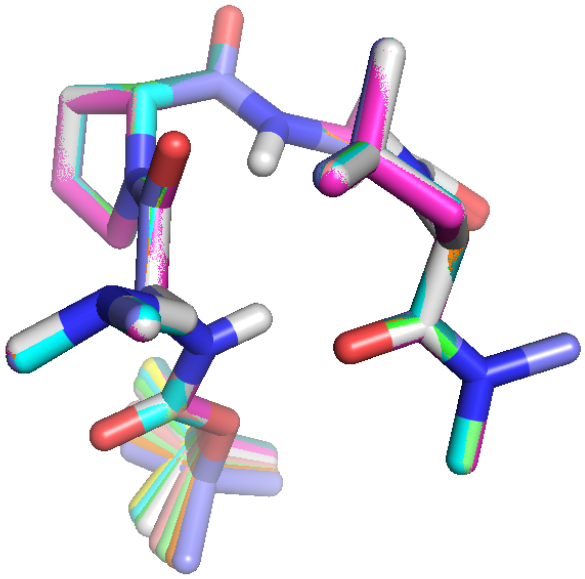


Table S2: NOESY-Derived Distances and Assignments for Peptide **4l**

	f2	f1	Normalized	Absolute	Assignment	Corrected Distances (Normalized)
1	7.93 5.81	5.81 7.94	-0.24 -0.24	-0.03 -0.03	LeuNH-DmaaNH	4.21
2	7.93 7.67	7.67 7.93	-1.27 -1.26	-0.18 -0.18	LeuNH-AcpcNH	3.19
3	7.93 1.53	1.53 7.93	-0.72 -0.7	-0.1 -0.1	LeuNH-BocMe	4.31
4	7.93 4.42	4.42 7.93	-0.55 -0.58	-0.08 -0.08	LeuNH-DProHA	3.70
5	7.67 1.53	1.53 7.67	-1.75 -1.75	-0.25 -0.25	AcpcNH-BocMe	3.70
6	7.67 1.42	1.42 7.67	-0.95 -0.9	-0.14 -0.13	AcpcNH-DProHC2	3.60
7	7.67 1.05	1.06 7.67	-4.47 -4.48	-0.64 -0.64	AcpcNH-AcpcHB1a	2.55
8	7.67 4.42	4.42 7.67	-1.76 -1.76	-0.25 -0.25	AcpcNH-DProHA	3.03
9	7.67 3.62	3.62 7.67	-1.63 -1.63	-0.23 -0.23	AcpcNH-DProHD2	3.04
10	7.67 1.18	1.18 7.67	-1.09 -1.11	-0.16 -0.16	AcpcNH-AcpcHB1b	3.32
11	7.67 1.66	1.66 7.67	-0.28 -0.28	-0.04 -0.04	AcpcNH-AcpcHB2a	4.18
12	5.82	2.45	-5.57	-0.8	DmaaNH-DmaaHB2	2.51

	2.45	5.83	-5.55	-0.8		
13	5.82 1.53	1.53 5.82	-0.91 -0.9	-0.13 -0.13	DmaaNH-BocMe	4.13
14	5.81 2.1	2.1 5.82	-1.35 -1.31	-0.19 -0.19	DmaaNH-DmaaHB1	3.15
16	5.06 0.99	0.99 5.06	-6.49 -6.57	-0.93 -0.94	LeuHA-LeuHD	2.73
17	4.1 3.62	3.62 4.1	-13.32 -13.33	-1.92 -1.92	DmaaHA-DProHD2	2.18
18	4.42 1.41	1.42 4.42	-0.19 -0.18	-0.03 -0.03	DProHA-DProHC2	4.62
19	4.1 2.91	2.91 4.1	-10.44 -10.38	-1.5 -1.49	DmaaHA-DProHD1	2.28
20	4.1 1.82	1.82 4.11	-7.1 -7.11	-1.02 -1.02	DmaaHA-DmaaMe	2.87
21	3.61 1.06	1.06 3.62	-0.27 -0.27	-0.04 -0.04	DProHD2-AcpcHB1a	4.10
23	2.91 1.61	1.62 2.91	-0.9 -0.96	-0.13 -0.14	DProHD1-DProHB1	3.31
24	2.91 2.11	2.11 2.91	-0.65 -0.64	-0.09 -0.09	DProHD1-DmaaHB1	3.60
25	2.44 1.82	1.82 2.44	-5.64 -5.64	-0.81 -0.81	DmaaHB2-DmaaMe	2.99
26	1.81 1.02	1.02 1.82	-6.61 -6.59	-0.95 -0.95	LeuHD(downfield)-DmaaMe	3.04
27	3.62 2.91	2.91 3.61	-40.93 -40.67	-5.89 -5.85	DProHD2-DProHD1	1.80

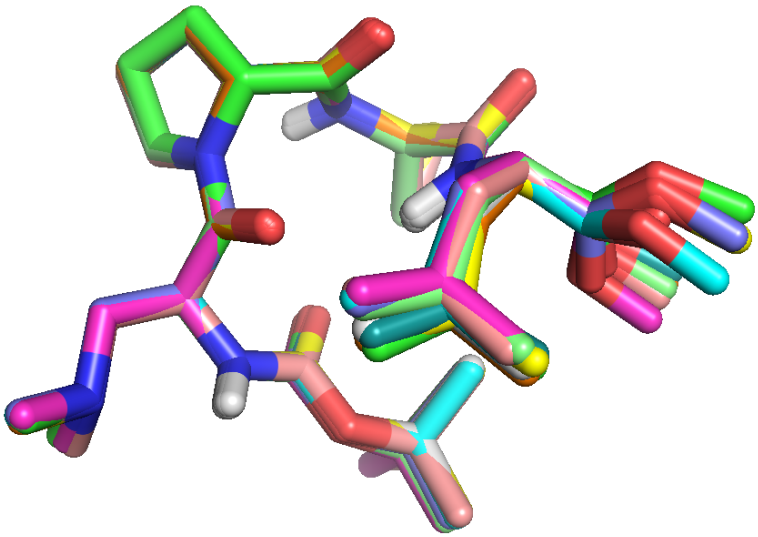
D. Ten Lowest-Energy Scored Structures from Simulated Annealing with CNS



RMSD Data for Peptide 3

Residue	Backbone RMS	Sidechain RMS
Boc	0.003	0.338
Dmaa	0.004	0.606
DPro	0.003	0.006
Acpc	0.013	0.026
Leu	0.007	0.013
NMe_2	0.004	0.007

Figure S2: Ten lowest-energy scored structures from simulated annealing of peptide **3** in CNS. The ensemble shows a high degree of homogeneity across all ten structures with the most variability being in the Boc *N*-terminal cap.



RMSD Data for Peptide 4l

Residue	Backbone RMSD	Sidechain RMSD
Boc	0.069	0.550
Dmaa	0.029	0.743
DPro	0.045	0.070
Acpc	0.040	0.060
Leu	0.067	0.525
OMe	0.000	1.322

Figure S3: Ten lowest energy-scored structures from simulated annealing of peptide **4l** in CNS. The ensemble shows a high degree of homogeneity across all ten structures with the most variability being in the methyl-ester *C*-terminal cap.

E. CNS Simulated Annealing Outputs

Table S3: CNS-Output Coordinates for Peptide **3***

Tag	Symbol	X	Y	Z
1	O	5.985	-1.441	-1.017
2	C	7.155	-1.126	-1.23
3	O	7.721	-0.944	-2.445
4	C	6.891	-0.866	-3.654
5	C	6.13	-2.179	-3.838
6	C	5.894	0.285	-3.52
7	C	7.812	-0.625	-4.842
8	H	6.683	-2.822	-4.505
9	H	5.158	-1.973	-4.258
10	H	6.011	-2.671	-2.882
11	H	5.058	0.111	-4.179
12	H	6.38	1.21	-3.789
13	H	5.541	0.347	-2.5
14	H	7.306	-0.004	-5.565
15	H	8.068	-1.571	-5.293
16	H	8.715	-0.129	-4.511
17	N	8.048	-0.929	-0.265
18	H	8.943	-0.611	-0.51
19	C	7.643	-0.847	1.132
20	H	6.565	-0.858	1.169
21	C	8.185	-2.055	1.901
22	H	9.226	-1.877	2.138
23	H	8.122	-2.923	1.264
24	N	7.491	-2.352	3.119
25	C	6.046	-2.508	2.955
26	H	5.846	-3.168	2.126
27	H	5.6	-1.542	2.765
28	H	5.623	-2.93	3.854
29	C	8.036	-3.502	3.84
30	H	7.52	-4.399	3.535
31	H	7.905	-3.353	4.903
32	H	9.086	-3.605	3.617
33	C	8.148	0.45	1.761
34	O	8.813	0.436	2.796
35	N	7.842	1.603	1.136
36	C	8.253	2.911	1.602
37	H	8.467	2.906	2.645
38	C	7.032	3.739	1.301
39	H	7.332	4.739	1.041
40	H	6.42	3.751	2.17
41	C	6.345	3.055	0.149
42	H	6.41	3.677	-0.73
43	H	5.311	2.87	0.399
44	C	7.065	1.747	-0.084
45	H	7.709	1.822	-0.945
46	H	6.367	0.938	-0.196
47	C	9.45	3.425	0.844
48	O	9.925	4.534	1.091
49	N	10.16	2.438	0.403
50	H	9.81	1.561	0.63
51	C	11.262	2.419	-0.587
52	C	11.92	3.734	-0.981
53	C	11.017	3.02	-1.964
54	H	11.498	4.688	-0.701
55	H	12.917	3.789	-1.388
56	H	11.574	2.7	-2.832
57	H	10.164	3.641	-2.183
58	C	12.183	1.223	-0.571
59	O	12.84	0.939	-1.572
60	N	11.993	0.388	0.447
61	H	11.666	0.745	1.294
62	C	12.356	-1.022	0.374
63	H	13.297	-1.133	-0.103
64	C	12.421	-1.679	1.739
65	H	13.444	-1.658	2.073
66	H	12.109	-2.713	1.617
67	C	11.554	-1.046	2.819
68	H	10.695	-0.583	2.358
69	C	11.058	-2.111	3.781
70	H	10.108	-1.809	4.194
71	H	11.775	-2.239	4.577
72	H	10.939	-3.044	3.247
73	C	12.341	0.028	3.546
74	H	11.682	0.839	3.815
75	H	13.121	0.397	2.893
76	H	12.785	-0.391	4.437
77	C	11.457	-1.806	-0.46
78	O	10.298	-2.057	-0.131
79	N	12.056	-2.368	-1.486
80	C	11.354	-3.226	-2.302
81	C	13.453	-2.114	-1.873
82	H	12.062	-3.759	-2.888
83	H	10.842	-3.884	-1.635
84	H	10.659	-2.683	-2.925
85	H	13.611	-1.052	-1.973
86	H	14.112	-2.509	-1.115
87	H	13.667	-2.596	-2.818

*Average of the 10 lowest-energy scored structures generated by CNS.

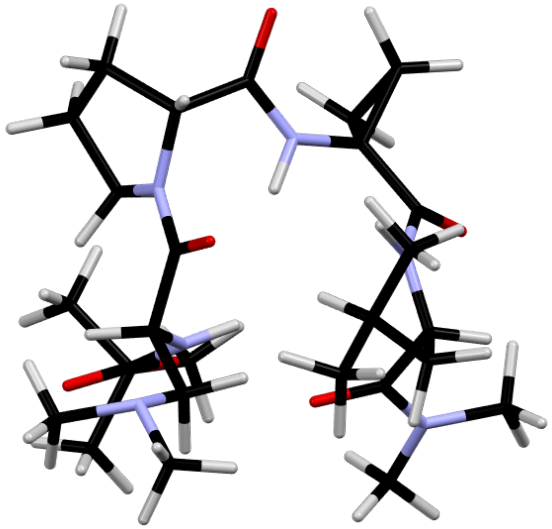
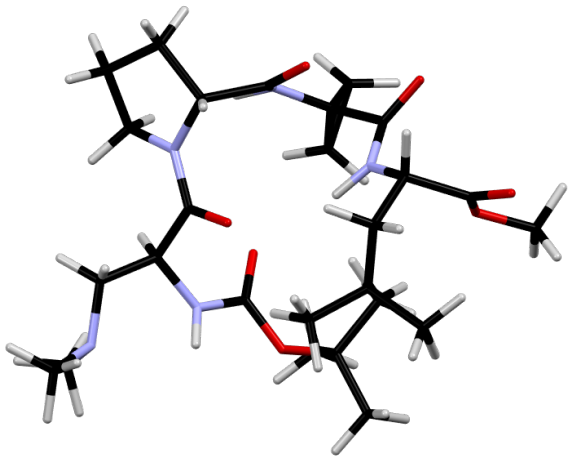


Table S4: CNS-Output Coordinates for Peptide **4l***

Tag	Symbol	X	Y	Z
1	O	6.988	0.569	-1.485
2	C	6.605	-0.598	-1.568
3	O	6.868	-1.451	-2.584
4	C	7.613	-0.999	-3.766
5	C	6.854	0.14	-4.446
6	C	8.996	-0.506	-3.343
7	C	7.746	-2.179	-4.718
8	H	7.252	0.293	-5.437
9	H	6.972	1.042	-3.866
10	H	5.804	-0.108	-4.515
11	H	9.698	-1.324	-3.395
12	H	8.948	-0.134	-2.332
13	H	9.321	0.287	-4.003
14	H	8.212	-1.849	-5.633
15	H	6.767	-2.576	-4.933
16	H	8.354	-2.95	-4.264
17	N	5.852	-1.188	-0.646
18	H	5.648	-2.141	-0.745
19	C	5.618	-0.559	0.647
20	H	5.262	0.444	0.468
21	C	4.554	-1.333	1.425
22	H	3.89	-0.625	1.897
23	H	5.039	-1.92	2.19
24	N	3.766	-2.221	0.626
25	C	2.762	-1.542	-0.189
26	H	1.872	-1.377	0.398
27	H	2.522	-2.154	-1.047
28	H	3.15	-0.591	-0.52
29	C	3.141	-3.299	1.389
30	H	3.905	-3.916	1.835
31	H	2.531	-3.899	0.727
32	H	2.524	-2.879	2.168
33	C	6.91	-0.488	1.457
34	O	7.747	-1.388	1.392
35	N	7.099	0.591	2.237
36	C	8.294	0.778	3.056
37	H	8.538	-0.115	3.61
38	C	7.905	1.905	4.03
39	H	8.509	2.778	3.83
40	H	8.071	1.576	5.045
41	C	6.454	2.181	3.781
42	H	6.263	3.241	3.868
43	H	5.85	1.632	4.487
44	C	6.173	1.715	2.382
45	H	6.395	2.494	1.669
46	H	5.149	1.391	2.286
47	C	9.489	1.193	2.211
48	O	10.631	0.863	2.532
49	N	9.236	2.117	1.291
50	H	8.322	2.466	1.225
51	C	9.98	2.107	0.003
52	C	10.162	3.422	-0.747
53	C	9.205	2.378	-1.28
54	H	9.629	4.318	-0.463
55	H	10.952	3.58	-1.464
56	H	9.539	2.006	-2.238
57	H	8.203	2.778	-1.281
58	C	11.115	1.133	-0.147
59	O	12.253	1.474	0.175
60	N	10.682	-0.121	-0.057
61	H	9.731	-0.312	-0.205
62	C	11.594	-1.227	0.213
63	H	12.165	-0.977	1.095
64	C	10.807	-2.512	0.478
65	H	10.162	-2.345	1.327
66	H	11.51	-3.294	0.728
67	C	9.945	-2.995	-0.69
68	H	9.649	-2.144	-1.287
69	C	10.735	-3.941	-1.581
70	H	10.505	-4.962	-1.316
71	H	11.792	-3.764	-1.447
72	H	10.469	-3.769	-2.614
73	C	8.683	-3.673	-0.175
74	H	8.843	-4.01	0.839
75	H	8.446	-4.519	-0.803
76	H	7.863	-2.97	-0.195
77	C	12.556	-1.436	-0.952
78	O	13.603	-2.071	-0.822
79	O	12.16	-0.75	-2.048
80	C	13.025	-0.818	-3.17
81	H	13.383	-1.828	-3.294
82	H	13.867	-0.161	-3.022
83	H	12.505	-0.52	-4.072

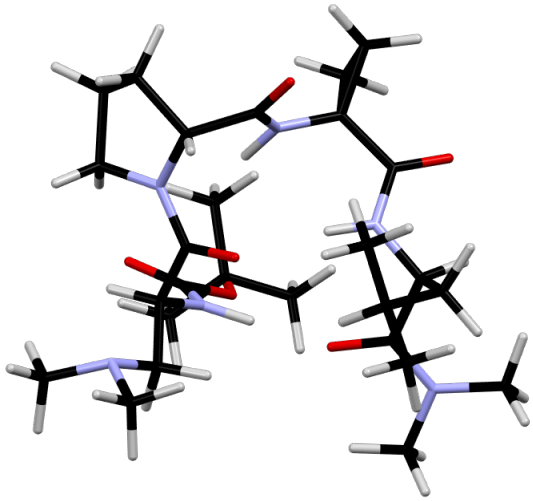
*Average of the 10 lowest-energy scored structures generated by CNS.



F. DFT-Optimization of the CNS Output for Peptides 3 and 4l

Table S5: Optimized Coordinates of Peptide **3** using B3LYP/6-31G(d,p)

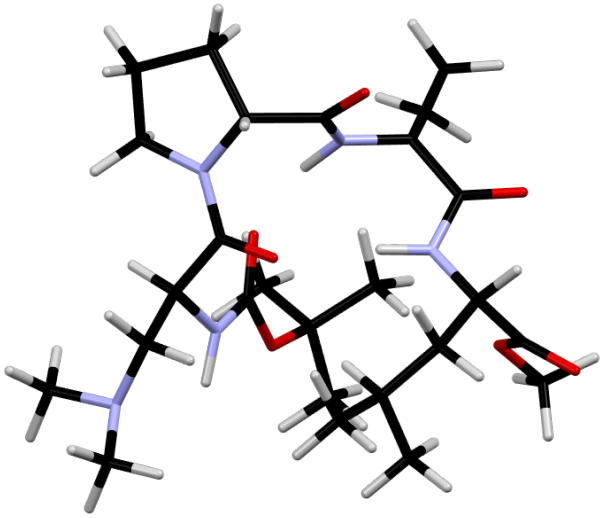
Tag	Symbol	X	Y	Z
1	O	3.543073	-1.293094	-0.646879
2	C	2.357681	-1.595117	-0.766759
3	O	1.808487	-2.788027	-0.438325
4	C	2.619676	-3.875842	0.132909
5	C	3.695996	-4.31157	-0.866473
6	C	3.21395	-3.439091	1.475815
7	C	1.586357	-4.986944	0.334369
8	H	3.23865	-4.574693	-1.825366
9	H	4.214653	-5.19623	-0.483595
10	H	4.425174	-3.517783	-1.029029
11	H	3.717806	-4.288076	1.948509
12	H	2.420266	-3.099452	2.149189
13	H	3.935829	-2.633428	1.340765
14	H	2.065942	-5.87183	0.762606
15	H	1.131274	-5.266564	-0.62
16	H	0.793506	-4.658852	1.012419
17	N	1.393016	-0.768313	-1.255489
18	H	0.419664	-1.072123	-1.24337
19	C	1.687983	0.587378	-1.699948
20	H	2.773484	0.676225	-1.729595
21	C	1.09403	0.860169	-3.089088
22	H	0.006689	0.806949	-2.997736
23	H	1.412024	0.059022	-3.778392
24	N	1.47185	2.194283	-3.55564
25	C	2.772211	2.207061	-4.215464
26	H	2.782087	1.634149	-5.162358
27	H	3.538796	1.780903	-3.56151
28	H	3.063008	3.238091	-4.440585
29	C	0.445684	2.810811	-4.388443
30	H	0.261229	2.26761	-5.334674
31	H	0.747507	3.831751	-4.644352
32	H	-0.493884	2.863911	-3.831938
33	C	1.073686	1.568498	-0.684456
34	O	-0.14225	1.795162	-0.686469
35	N	1.869855	2.080705	0.292021
36	C	1.27032	2.982321	1.289541
37	H	0.681256	3.756148	0.792018
38	C	2.494727	3.572786	2.027051
39	H	2.272064	3.793102	3.073133
40	H	2.785972	4.510869	1.543922
41	C	3.592171	2.513315	1.834266
42	H	3.465691	1.697889	2.554774
43	H	4.60129	2.914076	1.956087
44	C	3.342742	1.997793	0.41159
45	H	3.692651	0.975785	0.253668
46	H	3.818891	2.651622	-0.330752
47	C	0.274978	2.2932	2.242777
48	O	-0.519903	2.967812	2.885315
49	N	0.382094	0.932794	2.341785
50	H	1.038691	0.475803	1.723809
51	C	-0.494289	0.107949	3.121107
52	C	-0.600351	0.388925	4.606347
53	C	0.15891	-0.812732	4.147492
54	H	-0.054433	1.251989	4.966777
55	H	-1.580845	0.231462	5.040029
56	H	-0.302947	-1.785208	4.272931
57	H	1.243253	-0.788416	4.191314
58	C	-1.73917	-0.45159	2.464323
59	O	-2.504018	-1.173537	3.111593
60	N	-1.943221	-0.138176	1.157245
61	H	-1.282153	0.435898	0.643504
62	C	-3.07787	-0.689807	0.436976
63	H	-3.535358	-1.385389	1.142712
64	C	-4.137868	0.377649	0.054945
65	H	-4.570759	0.7517	0.99016
66	H	-4.949994	-0.140264	-0.468976
67	C	-3.634585	1.567515	-0.80678
68	H	-2.697272	1.275008	-1.29428
69	C	-4.650207	1.906155	-1.909277
70	H	-4.306252	2.750065	-2.51715
71	H	-5.620862	2.182946	-1.478942
72	H	-4.813918	1.054964	-2.580059
73	C	-3.345702	2.808044	0.053373
74	H	-2.92902	3.61624	-0.556807
75	H	-2.633175	2.59831	0.854369
76	H	-4.269769	3.178754	0.515292
77	C	-2.575769	-1.452742	-0.804606
78	O	-1.488465	-1.159663	-1.318267
79	N	-3.377233	-2.415965	-1.342822
80	C	-2.961095	-3.083102	-2.573046
81	C	-4.651045	-2.879099	-0.806303
82	H	-3.733366	-2.967976	-3.342322
83	H	-2.030747	-2.638412	-2.917797
84	H	-2.809687	-4.153777	-2.392557
85	H	-4.630675	-3.97039	-0.708979
86	H	-4.855993	-2.457551	0.173872
87	H	-5.475059	-2.612945	-1.479622



Summary
Calculation Type = FREQ
Calculation Method = RB3LYP
Basis Set = 6-31G(d,p)
Charge = 0
Spin = Singlet
E(RB3LYP) = –1837.78766095 a.u.
RMS Gradient Norm = 0.00000318 a.u.
Imaginary Freq = 0
Dipole Moment = 5.2735 Debye
Point Group = C1

Table S6: Optimized Coordinates of Peptide **4l** using B3LYP/6-31G(d,p)

Tag	Symbol	X	Y	Z
1	O	1.080039	0.290934	1.961257
2	C	1.098664	-0.91055	1.684324
3	O	0.452624	-1.888753	2.342655
4	C	-0.41204	-1.608533	3.507354
5	C	0.442969	-1.070898	4.657969
6	C	-1.53902	-0.649914	3.115741
7	C	-0.968511	-2.994703	3.839985
8	H	-0.179112	-0.94416	5.549542
9	H	0.881704	-0.106413	4.39922
10	H	1.245118	-1.774906	4.900307
11	H	-2.024771	-0.98264	2.194352
12	H	-1.16518	0.361458	2.961116
13	H	-2.287702	-0.627275	3.914132
14	H	-1.61774	-2.934598	4.718145
15	H	-0.157606	-3.696236	4.05595
16	H	-1.552033	-3.387438	3.002457
17	N	1.793402	-1.427558	0.637598
18	H	1.903133	-2.432215	0.556198
19	C	2.766459	-0.636348	-0.092953
20	H	3.547898	-0.292829	0.590885
21	C	3.373629	-1.527429	-1.195399
22	H	4.208886	-0.981715	-1.671545
23	H	2.60066	-1.674099	-1.954294
24	N	3.774429	-2.838491	-0.688053
25	C	4.965759	-2.77774	0.157087
26	H	5.853	-2.39801	-0.381886
27	H	5.197638	-3.778661	0.531573
28	H	4.7897	-2.133387	1.022765
29	C	3.951248	-3.800489	-1.775089
30	H	3.030074	-3.873952	-2.359751
31	H	4.169786	-4.787112	-1.356102
32	H	4.774443	-3.530564	-2.460646
33	C	2.074903	0.570696	-0.759764
34	O	1.134449	0.389815	-1.542433
35	N	2.523308	1.813334	-0.464553
36	C	1.871156	2.990513	-1.067166
37	H	2.033045	2.98888	-2.149418
38	C	2.585541	4.184221	-0.392161
39	H	2.037726	4.474322	0.511116
40	H	2.627347	5.051559	-1.052778
41	C	3.963272	3.626327	-0.014357
42	H	4.451226	4.192014	0.783057
43	H	4.627346	3.627795	-0.885367
44	C	3.659658	2.182845	0.405094
45	H	3.363473	2.114056	1.458588
46	H	4.514806	1.523971	0.242066
47	C	0.351233	3.094598	-0.884355
48	O	-0.295366	3.761429	-1.683725
49	N	-0.184776	2.518707	0.232992
50	H	0.368807	1.873145	0.791844
51	C	-1.590771	2.618876	0.508341
52	C	-2.140908	3.986215	0.85994
53	C	-1.996791	2.95855	1.935817
54	H	-1.432288	4.805425	0.824731
55	H	-3.137188	4.199227	0.491405
56	H	-2.895669	2.474922	2.301656
57	H	-1.190867	3.066059	2.655046
58	C	-2.541041	1.713341	-0.245183
59	O	-3.761885	1.867084	-0.156548
60	N	-1.99645	0.719052	-0.99631
61	H	-0.991338	0.663957	-1.127354
62	C	-2.867953	-0.041353	-1.877758
63	H	-3.487817	0.669033	-2.437763
64	C	-2.073017	-0.850499	-2.926696
65	H	-1.493098	-0.11487	-3.496244
66	H	-2.8074	-1.274943	-3.621486
67	C	-1.117541	-1.966792	-2.450361
68	H	-0.487865	-1.570091	-1.645381
69	C	-1.844899	-3.216165	-1.92973
70	H	-2.534255	-3.616349	-2.682946
71	H	-2.414973	-3.011769	-1.021112
72	H	-1.122773	-4.004459	-1.68887
73	C	-0.182992	-2.342712	-3.611593
74	H	-0.751924	-2.709077	-4.47541
75	H	0.510303	-3.138028	-3.314793
76	H	0.409117	-1.481506	-3.937378
77	C	-3.920999	-0.889307	-1.158335
78	O	-4.919807	-1.282306	-1.725609
79	O	-3.637376	-1.17914	0.126417
80	C	-4.658019	-1.923404	0.816874
81	H	-4.807472	-2.898764	0.347754
82	H	-5.60059	-1.372533	0.80543
83	H	-4.296319	-2.041117	1.837611



Summary
Calculation Type = FREQ
Calculation Method = RB3LYP
Basis Set = 6-31G(d,p)
Charge = 0
Spin = Singlet
E(RB3LYP) = –1818.33861237 a.u.
RMS Gradient Norm = 0.00000346 a.u.
Imaginary Freq = 0
Dipole Moment = 13.3420 Debye
Point Group = C1

VI. Crystallographic Information

A. Experimental

Low-temperature diffraction data (ω-scans) were collected on a Rigaku MicroMax-007HF diffractometer coupled to a Saturn994+ CCD detector with Cu Kα (λ = 1.54178 Å) for the structures of **3(c)** and **4l**. The diffraction images were processed and scaled using the Rigaku CrystalClear software.[13] The structure was solved with SHELXT and was refined against F^2 on all data by full-matrix least squares with SHELXL.[14] All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in the model at geometrically calculated positions and refined using a riding model. Unless stated otherwise, the isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the U value of the atoms to which they are linked (1.5 times for methyl groups). The full numbering scheme of compound **3(c)** and **4l** can be found in Figures S4 and S5, respectively. Full details of the X-ray structure determination are in the CIFs included as Supporting Information. CCDC number 1453125 (**3(c)**) and 1453124 (**4l**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center *via* http://www.ccdc.cam.ac.uk/data_request/cif.

Data and Refinement Details for 3c

The only exceptions are hydrogen atoms H2, H3 and H5, which are freely refining and a part of refined hydrogen bond interactions.

Data and Refinement Details for 4l

Multiple attempts to collect data at 93 K resulted in streaky reflections. The data reported here were collected at 228 K, which obscured the already difficult to locate hydrogen atoms associated with the heteroatoms. The model reported here uses riding models and geometrically placed hydrogen atoms on heteroatoms. The ester and butyl residues are disordered over two equally occupied positions. The atoms involved are distinguished with the suffix "a" and "b". The atomic displacement parameters are large (due to the relatively high temperature need for data collection). Subsequently, rigid bond restrains were used to aid the refinement.

Table S7: Details of X-Ray Crystal Structures **3(a–c)** and **4l**

Compound	**3(a,b)***	**3(c)**	**4l**
Data Code	007-15050	007-15126	007-15146
Empirical Formula	$C_{27}H_{49}N_6O_{6.5}$	$C_{27}H_{48}N_6O_6$	$C_{26}H_{44}N_5O_7$
Temperature (K)	93(2)	93(2)	228(2)
FW	561.72	552.71	538.66
Crystal System	Monoclinic	Orthorombic	Orthorombic
Space Group	$P2_1$	$P2_12_12_1$	$P2_12_12_1$
***a* (Å)**	16.1717(11)	11.7899(8)	11.9360(8)
***b* (Å)**	9.364(6)	15.9908(11)	16.0501(11)
***c* (Å)**	21.5606(15)	16.3363(11)	16.5597(12)
α (deg)	90	90	90
β (deg)	104.7162(2)	90	90
γ (deg)	90	90	90
***V* (Å^3)**	3157.9(4)	3079.9(4)	3172.4(4)
Z	4	4	4
ρ (g/cm^3)	1.181	1.192	1.128
μ (mm^{-1})	0.693	0.691	0.676
Absolute Structure Parameter	–0.04(15)	0.01(4)	-0.01(3)
***R*1, w*R*2 (I > 2*s*(I))**	0.0651, 0.1665	0.0287, 0.0784	0.0504, 0.1454
***R*1, *wR*2 (all data)**	0.9082, 0.1864	0.0307, 0.0792	0.0534, 0.1513
GOF	1.023	1.060	1.023
Largest Diff. Peak, Hole (e A^{-3})	0.760, –0.285	0.274, –0.166	0.280, –0.190

*Data reported in ref. 6 (CSD entry 1412920).

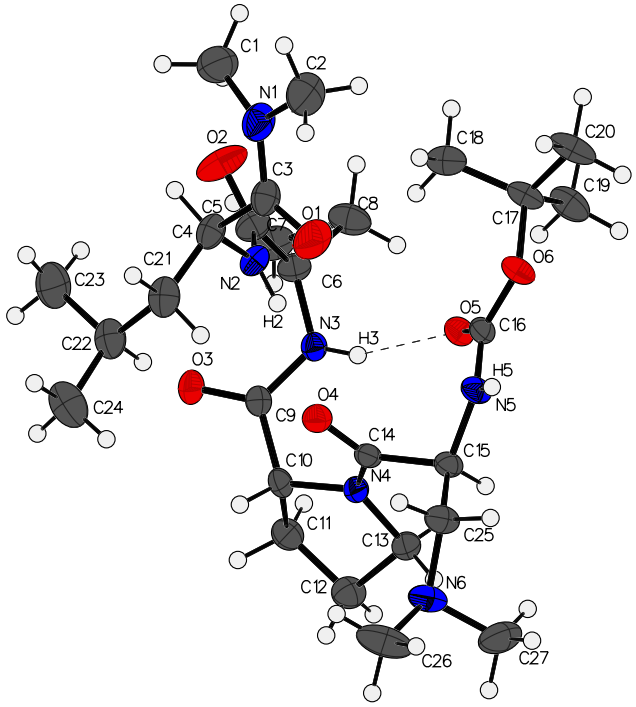


Figure S4: The full numbering scheme of **3(c)** with 50% thermal ellipsoids. The hydrogen atoms are depicted as circles for clarity.

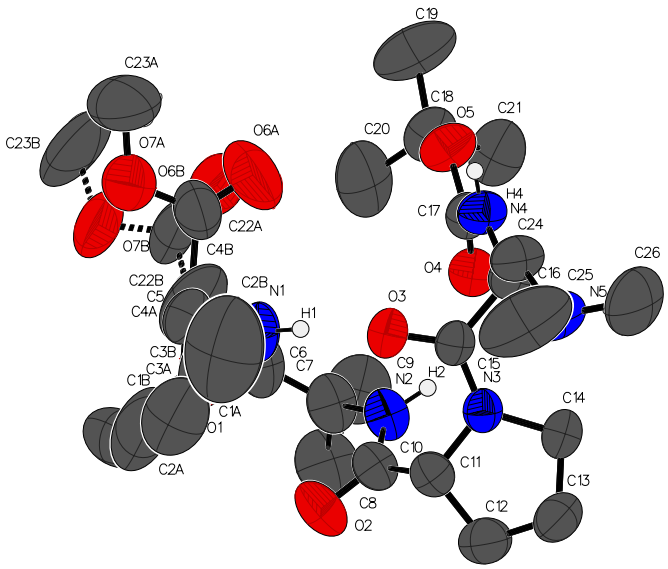


Figure S5: The full numbering scheme of **4l** with 50% thermal ellipsoids. Most of the hydrogen atoms are either not shown or depicted as circles for clarity.

B. Definition of Planes Describing Backbone Bending in Conformers 3(a,b)

To describe the degree of backbone-bending observed in the type II' β-turn conformers of peptide **3**, we measured the angle between two defined planes, which were calculated using the program Mercury (Figure S6).[15] For both conformers **3(a)** and **3(b)**, Plane 1 was defined by the α-carbons of *i*, *i*+1, *i*+2, and *i*+3, and Plane 2 was defined by the α-carbons of *i*, *i*+3 (*trans*-Me C-atom of the NMe_2-group) *i*+4, and *i*–1 (3º C-atom of the Boc-group).

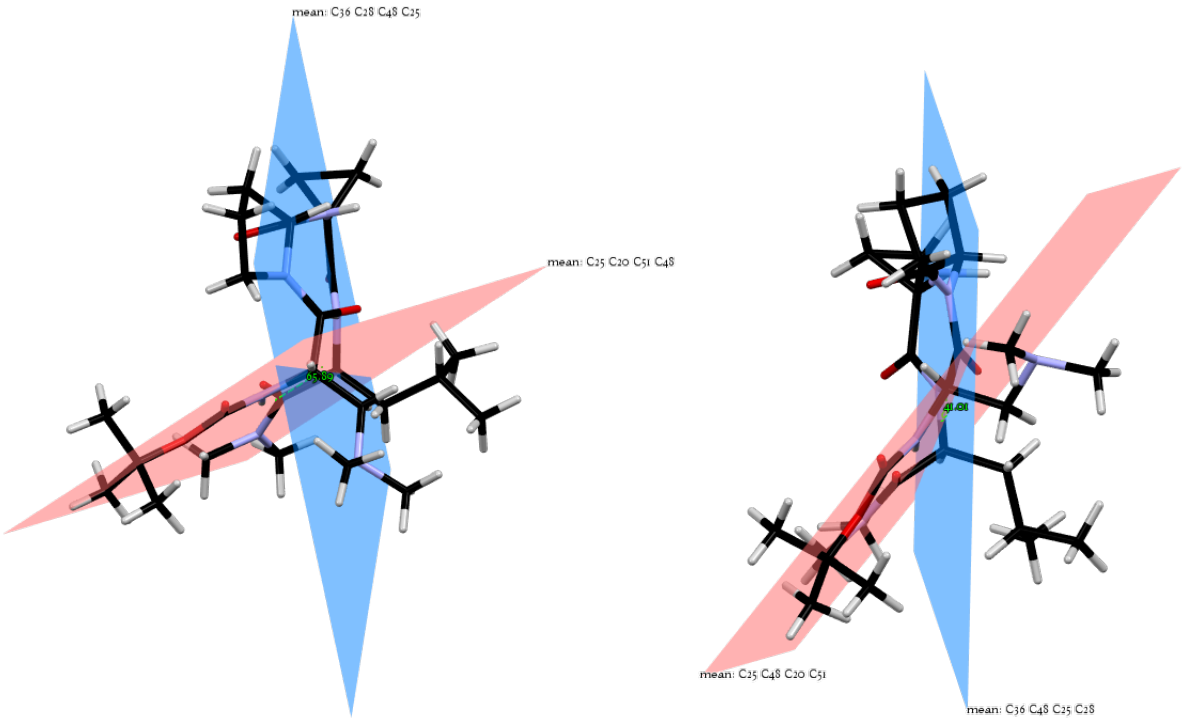


Figure S6: Intersecting planes that describe the backbone bending of conformers **3(a)** (left) and **3(b)** (right). The backbone bend of **3(a)** was measured to be 65.9º, while the bend of **3(b)** was measured to be 41.0º.

VII. References

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